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INVESTIGATION OF EXAGGERATED WHEEL RUNNING IN ALBINO RATS: EFFECTS OF PRE-ADAPTATION TO A RESTRICTED FEEDING SCHEDULE AND DAILY TREATMENT WITH CIMETIDINE

by

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INTRODUCTION

Considerable experimental evidence suggests that food deprivation naturally induces locomotor arousal (Campbell, 1964; Campbell & Misanin, 1969). The amount of increase in activity has been observed to vary depending on the type of apparatus used (Strong, 1957; Treichler & Hall, 1962). Historically, 3 general measures of activity have been employed. These measures include activity wheels, stationary cages which use photoelectric cells or microswitches to record movement, and mazes which measure more extended locomotor activity (Treichler & Hall, 1962). Apparently, different measuring devices do not measure the same events (Reed, 1947) and do not yield interchangable data (Weasener, Finger, & Reid, 1960). Strong (1957) concluded that hunger primarily leads to an increase in gross locomotor activity (measured by revolutions/day in an activity wheel); but that hunger leads to a decrease in fine, essentially non-locomotor movements (measured in mazes or with stablimeters). When activity was measured in activity wheels, severe loss or body weight was observed; but when activity during restricted food access was measured using mazes or stablimeters, no drastic decrease in body weight was observed.

Exaggerated locomotor arousal induced by food

deprivation had been repeatedly observed by many investigators when an animal was housed in an activity wheel and activity was measured in revolutions per day (Campbell & Misanin, 1969; Cornish & Mrosovsky, 1965; Hall, 1956; Hall & Hanford, 1955; Moskowitz, 1959; Routtenberg, 1968). If maintained, wheel running eventually becomes excessive, leads to ulceration of the glandular stomach, and culminates with inanition and the ultimate demise of the rat (Pare & Houser, 1973). Excessive running appears to be the result of an interaction between having access to a running wheel and being on a restricted feeding schedule. When an animal was housed in an activity wheel and maintained an an ad-lib diet, there was no great increase in running activity, body weight stablized, and no ulceration of the glandular stomach was observed (Pare & Houser, 1973). Additionally, if an animal did not have access to a running wheel and was fed for 1 hour per day, body weight stablized within 15 to 20 days (Routtenberg & Kuznesof, 1967), ulcers did not form, spontaneous activity did not substantially increase (Finger, 1951; Hall, Smith, Schnitzer, & Hanford, 1953; Moskowitz, 1959; Routtenberg, 1968), and no other adverse effects were observed. Therefore, it appears that excessive wheel running was triggered through a unique interaction which results when

an animal had free access to a running wheel and was maintained on a restricted feeding schedule.

Accompanying excessive running was the development of ulcers in the glandular portion of the rat's stomach (Pare, 1980; Pare & Houser, 1973). These glandular ulcers are considered to be similar to the peptic or "stress" ulcers observed in humans (Pare, 1980). If running activity did not become elevated, glandular ulceration was usually not observed (Pare & Houser, 1973). Animals on an ad-lib diet and housed in an activity wheel failed to develop glandular ulceration (Glavin & Mikhail, 1975). Further, animals which were food deprived and did not have access to a running wheel did not develop ulcers in the glandular portion of the stomach but did occasionally develop ulcers in the rumenal portion of the stomach. Ulcers in the rumen were referred to as "starvation ulcers" and were considered to be difrerent etiologically from glandular ulcers (Glavin & Mikhail, 1976a; Mikhail, 1971; Mikhail & Hirschberg, 1972). Therefore, it appears that glandular ulceration is also the result of a unique interaction between being maintained on a one hour feeding schedule and having free access to a running wheel.

The purpose of the following studies was to examine the role that a restricted feeding schedule and

ulcerogenesis play in either instigating excessive wheel running and/or in maintaining high levels of activity during times of food deprivation and severe body weight loss. The experimental combination of free access to a running wheel while on a restricted feeding schedule is descriptively referred to as the activity-deprivation procedure in the ensueing discussion.

BEHAVIORAL CHARACTERISTICS

When a rat has free access to a running wheel and experiences a one hour per day food deprivation schedule, a unique behavioral and physiological pattern emerges over the course of the experiment (Campbell & Sheffield, 1953; Hall, 1956; Hall & Hanford, 1955; Moskowitz, 1959; Pare, 1976; Routtenberg, 1968; Routtenberg & Kuznesof, 1967). During the first several days after introduction to the activity-deprivation schedule, a rat exhibits low levels to normal levels of running activity (approximately 1000 to 3000 revolutions per day). With each passing day, the rat progressively increases its running activity until it is running approximately 3 to 7 times above baseline levels. After 3 to 8 days of this schedule, running activity peaks and declines back toward baseline levels. The decline in activity signals the imminent death of the animal due to the debilitating effects of starvation and the large expenditure of energy

required for running.

Accompanying excessive running are progressively declining body weights. Indeed, excessive running appears to be only triggered after approximately 10 to 20 percent of body weight is lost (Hall & Hanford, 1955; Routtenberg & Kuznesof, 1967; Spatz & Jones, 1971). Negative correlations between increased running and decreased body weight are reported to range from -.57 to -.97 (Moskowitz, 1959; Treichler & Hall, 1962).

Food intake is also reduced below baseline values by rats which run excessively. Decrements in food intake can range from slight decreases to drastic reductions in the daily amount of food consumed per day. Routtenberg (1968) and several other investigators (Spatz & Jones, 1971; Strutt & Stewart, 1970) described the rat's behavior on an activity-deprivation schedule as self-starvation because the animal "chooses" to reduce food intake and to run excessively. Instead of self-starvation, reduction in food intake should probably be viewed as an indirect consequence of the experimental situation. Review of the literature in conjunction with observations from pilot studies indicated that reduced food intake by rats on activity-deprivation schedules is usually not as severe as reported by Routtenberg (1968) or at least comparable to the reduction in food intake by

control animals which are maintained on a 1 hour per day feeding schedule and housed in home cages. Initially, decreases in the amount of food consumed can be attributed to lack of familiarity with the 1 hour feeding schedule (Glavin, 1978; Seiser & Kackinnon, 1976), or to introducton into a novel environment (Routtenberg, 1968; Spatz & Jones, 1971).

ROLE OF RESTRICTED FEEDING SCHEDULES

Both psychological and physiological consequences of a restricted feeding schedule have been explored to explain the rat's paradoxical energy expenditure in times of food deprivation and severe body weight loss. Historically, the effects of a restricted feeding schedule on an animal's behavior have been discussed as either increasing motivational drive strength and thus increasing activity (Hall, 1956; Hall & Hanford, 1955; Hall et al., 1953; Moskowitz, 1959), or as a stressful event leading to ulcerogenesis (Pare, 1976, 1980; Vincent & Pare, 1976). Presently, no theory exists which can adequately explain what triggers and what maintains the rat's high rate of wheel running.

When increased activity following transition from unlimited feeding to a 23 hour deprivation schedule was first observed in the rat, the motivational variable of "drive state" was posited to explain the elevation in

activity (Finger, 1951; Hall, 1956; Hall & Hanford, 1955). Two hypotheses for increased drive state leading to increased activity were proposed. Hall and Hanford (1955) and other investigators concluded that once a certain percentage of body weight was lost (between 10 percent and 20 percent), increases in drive strength led to systematic increases in running activity. Furthermore, this energizing function of increased drive state was considered to be sufficient to explain the increases in activity when an animal was switched from an ad lib feeding schedule to a restricted feeding schedule.

Campbell and Sheffield (1953) hypothesized that, through increasing drive strength, thresholds for external stimulation were lowered. Increases in activity would only be observed if environmental stimulation increased, regardless of deprivation level. Hall and Hanford (1955) finally concluded that increased environmental stimulation led to an increase in activity and that addition of a food-deprivation schedule led to even greater increases in activity.

More recently, several investigators attempted to account for exaggerated running in terms of Amsel's Frustration Theory (Pare, 1974; Tsuda et al., 1982). It was suggested that rats exhibited excessive running due to frustration created by a restricted feeding schedule.

Central to Amsel's Theory is that frustration increases the vigor of a response and also leads to response persistence (Amsel, 1958). Therefore, Pare (1974) suggested that when food was removed from the running wheel cage, an internal aversive state of frustration was created which led to the persistence of running. In an attempt to reduce any "frustration" associated with the running wheel, rats were transfered to home cages for the 1 hour feeding period. Contrary to predictions, the home-cage fed rats ran more each day and ulcer development was exacerbated when compared to animals fed in activity wheels. As with previous motivational theories, Pare's application of Amsel's frustration theory failed to account for the excessive running demonstrated by food-deprived rats. If any explanation is to be found, psychological theories of motivation should become secondary and physiological theories concerning the effects of both food deprivation and effects of activity should be primary topics of study.

PHYSIOLOGICAL FACTORS ASSOCIATED WITH A RESTRICTED FEEDING SCHEDULE

Physiological effects on a rat maintained on a restricted feeding schedule include purely physical consequences such as "emptiness of the gut" (Hamilton, 1969) and purely metabolic consequences such as increased

lipogenesis (Leiveille, 1967). One physical consequence of a single feeding session lasting one hour is that, as time passes from the period of feeding, the stomach becomes increasingly empty and remains empty for relatively longer periods of time than the animal normally experiences.

If merely the reduction of the amount of food in the stomach leads to elevated activity, and not to any metabolic consequences of food deprivation, then a non-nutritive bulk substance should counter stomach emptiness without altering any metabolic consequences of a restricted feeding schedule. While permitting rats free access to a running wheel, Hamilton (1969) completely deprived animals of food for up to five days. One-half of these animals were given free access to a non-nutritive bulk substance during the 5 days of fasting. In animals which ate the non-nutritive bulk substance, running was initially suppressed below baseline levels for the first three days of the experiment. On the fourth and fifth days, running activity increased but peaked far below the increase observed in fasting, no-bulk animals. Subsequent experiments demonstrated that if the non-nutritive bulk was removed after the first three days of the experiment, running activity doubled. Correspondingly, if animals

were given access to the bulk substance after 3 days of fasting, running activity showed a sharp decline. Therefore, Hamilton (1969) suggested that excessive wheel running could be initially triggered by physical sensations originating from an empty stomach.

Studies on the effects of divided feeding schedules by Tsuda, Tanka, Iimori, Ida, & Nagasaki (1981) also supported the hypothesis that wheel running was initially due to the degree of emptiness of the stomach. Rats which had free access to running wheels and fed with divided feeding schedules of 1/2 hour:1/2 hour and 1 hour:1 hour did not exhibit excessive wheel running and developed few glandular ulcers. Animals fed in single feeding sessions lasting 1 hour or 2 hours ran excessively and developed extensive glandular ulceration. Extended feeding periods lasting up to 3 hours tended to decrease ulcer incidence but not significantly. Only animals in the single feeding session lasting 1 hour showed slightly lower food consumption when compared to the daily amount of food eaten by animals on either the divided feeding schedules or single feeding sessions lasting more than 1 hour.

Studies investigating the metabolic changes which occurred when an animal was switched from an ad-lib feeding schedule to a restricted feeding schedule

illustrated that rats fed for only 1 hour or 2 hours each day were capable of efficiently altering metabolism to adapt to a single feeding session. Leveille and O'Hea (1967) reported that animals fed for 2 hours each day (meal-fed rats) utilized food more efficiently than did ad-lib fed animals. Furthermore, these researchers suggested that the greater efficiency of the meal-fed rat was due to a reduction in activity and thus a reduction in energy expenditure. Additionally, Leveille and Chakrabarty (1967) reported that meal-fed rats were more efficient in storing calories in the form of tissue glycogen, a substance which serves as a storage of energy for meal-fed rats. It appears that the effects of a restricted feeding schedule operating alone serves to increase metabolic efficiency through decreasing energy expenditure. Therefore, it seems reasonable to conclude that the heightened activity observed in rats during the activity-deprivation rats is probably not a consequence of metabolic changes induced through food deprivation alone.

PRE-ADAPTATION TO A RESTRICTED FEEDING SCHEDULE

Some experimenters hypothesized that rats in the activity-deprivation situation never adapted to the single hour feeding session. The relationship between pre-adapatation to a restricted feeding schedule and

elevated running activity is not clear (Pare, 1980) as conflicting results have been reported. Pare, Vincent, Isom, and Reeves (1978) pre-adapted animals to a 1 hour per day feeding schedule for 15 days before the animals were placed in running wheels. Animals habituated to the restricted feeding schedule tended to eat more food and survived longer than did non-habituated animals. In habituated animals a mean number of 13 stomach lesions with a mean length of 35.5 mm were observed. Non-habituated animals had a mean number of 20 stomach lesions which averaged 49.5 mm in length; however no stastically significant difference in ulcer severity was indicated. Glavin (1978) habituated animals for either 7 days or 14 days to a restricted feeding schedule before entrance into the wheels. No significant differences in activity or ulcer severity between habituated and non-habituated animals were observed. However, Seiser and Kackinnon (1976) reported that animals habituated to a restricted feeding schedule for 33 days prior to entrance into the activity wheels failed to develop ulcers or to run excessively. Presently, it is unknown what the conclusive effects of prior adaptation to restricted feeding schedules have on either running wheel activity or on the formation of gastric lesions.

ROLE OF ULCEROGENESIS

In virtually all animals which showed high levels of running activity, glandular ulceration was observed (Pare & Houser, 1973). Correspondingly control animals which did not have access to running wheels rarely showed signs of ulceration in the glandular stomach (Pare, 1980). Presently, it is known that if running activity remains near baseline levels, glandular ulcers do not form; but it is not known if the process of ulcerogenesis triggers excessive running or if excessive running and glandular ulceration are simultaneously triggered through changes in the functioning of peripheral or central mechanisms. Due to the high correlations reported between glandular ulceration and excessive activity, it is essential to investigate both the etiologies of ulcer formation and the possible implications of the ulcerogenesis process in triggering the onset of exaggerated wheel running.

RUMENAL VERSUS GLANDULAR ULCERS

In rats, different experimental procedures lead to ulceration of two distinct regions of the rat's stomach, either in the rumenal portion or in the glandular portion (Glavin & Mikhail, 1975; Mikhail, 1971; Mikhail & Hirschberg, 1972). It is thought that the primary pathological agent in both rumenal ulcers and corpus ulcers is increased gastric acidity within the stomach

(Glavin & Mikhail, 1975). Ulcers occuring in the non-glandular portion of the stomach, the rumen, are considered to be "starvation ulcers" because severe ulceration of the rumen usually only occurs during times of food deprivation. The technique of pylorous ligation will also inherently cause ulceration of the rumen (Mikhail, 1971; Pare & Temple, 1973; Sawrey, 1956; Sawrey, Conger, & Turrel, 1956).

Ulceration of the glandular portion of the stomach (the corpus) occurs only if food deprivation is paired with some other "stressor" such as shock, restraint, refrigeration, or high activity (Glavin & Mikhail, 1975, 1976a; Pare, 1980). Therefore, only those experiments which predominately report ulceration in the glandular stomach are utilized to extrapolate information and to gain insight into the effects of the ulcerogenesis process on the triggering excessive wheel running in food deprived animals.

ETIOLOGY AND PREVENTION OF ULCER FORMATION

Although the presence of both food deprivation plus an additional "stressor" is crucial for the formation of glandular ulcers, it is not during the time of exposure to the "stressor" that ulcers are formed. Rather, it appears that a "poststress" rest period following a "stressful" event such as shock is necessary before

glandular ulcers begin to form. Desiderato, Mackinnon, & Hissom (1974) varied "poststress" delay (0, 2, 6, 12, 24 hours) periods following a brief shock session. Results indicated that ulcer formation did not occur in the 0 hour group but first appeared in the 2 hour "poststress" group. No progressive increase in the number of ulcers or ulcer severity was observed as the length of the "poststress" delay period increased beyond 2 hours. Therefore, Desiderato et al. (1974) suggested that ulcer formation may not be strictly time dependent and that any rest period could be sufficient to promote ulcerogenesis. Other studies reported formation of glandular ulcers when the procedure incorporated a 2 hour "poststress" rest period before sacrifice (Glavin & Mikhail, 1976a; Seiser & Houser, 1974), whereas researchers which reported no formation of glandular ulcers sacrificed their animals immediately following shock termination (Pare & Temple, 1973).

To explain the process of ulcerogenesis during the poststress rest period, the following hypotheses have been proposed: According to Desiderato et al. (1974), an exaggerated rebound of the parasympathetic system occurs following high sympathetic activity evoked during shock or refrigeration. This activation of the parasympathetic system is thought to lead to increased release of gastric

acid into the rat's stomach which is the critical factor instigating ulcer formation. Studies in which animals were switched from the running wheel to home cages for the hour feeding period reported that this manipulation exacerbated ulcer development because the home cage signaled a "safe environment" and evoked further rebound of the parasympathetic system and greater gastric acid secretions (Desiderato et al., 1974; Pare, 1974; Tsuda et al., 1982a).

If parasympathetic activity was blocked following exposure to "stress" and high sympathetic activity, glandular ulceration was prevented. When injections of scopolamine methybromide, a parasympathetic blocking agent thought to decrease gastric acid secretions, were administered immediately following termination of shock, ulcer incidence was significantly decreased (Seiser & Houser, 1974). When antagonistic sympathetic activity was evoked (through electical stimulation of the lateral hypothalmus) during the 2 hour "poststress" rest period, the animal was completely protected from glandular ulceration (Marshall & McCutchen, 1976). Additionally, if intraperitoneal injections of chlorpromazine (CPZ), a peripheral acting parasympathetic blocker, were administered preceding exposure to shock, ulcer incidence was decreased in an "all-or-none" protective fashion

(Shemberg, Green & Gliner; 1970). In the above studies, blockage of parasympathetic activity was thought to decrease ulcer incidence through inhibition of acid secretions during the "poststress" rest period (Levine & Senay, 1970; Seiser & Houser, 1974).

According to Wozniak and Goldstein (1980), the ulcerogenic effects of increased gastric acid secretions following "stress" termination were critically dependent on how empty the stomach was at the time of exposure to "stress". Manipulation of hours of deprivation (0, 9, 18, 48, or 144 hours of food deprivation) before exposure to 3 hours of cold-restraint "stress" indicated that groups pre-fed just prior to exposure to cold and restraint exhibited significantly less severe glandular ulceration. Wozniak and Goldstein (1980) hypothesized that less severe ulceration in the pre-fed groups was due to the presence of food in the stomach which protected the stomach walls from high gastric secretions triggered following stress termination.

Other studies suggested that food deprivation initially lead to an increase in gastric acid secretions (Glavin & Mikhail, 1975, 1976b; Levine & Senay, 1970). When an antacid drug, aluminum hydroxide, was given during the period of food deprivation prior to "restraint stress", both the incidence and severity of glandular

ulceration was reduced (Glavin & Mikhail, 1976b). Animals which were food deprived but force-fed aluminum hydroxide only during the restraint period and animals which received no antacid drug exhibited extensive and severe glandular ulceration. On the basis of these results, Glavin and Mikhail (1976b) suggested that food deprivation experienced prior to "restraint stress" increased stomach acidity which, if prevented, would ultimately reduce ulceration resulting from addition of a subesequent "stressor". If the heightened gastric acid secretions resulting from food deprivation remained unaltered, then the occurence and the severity of glandular ulceration were exacerbated through addition of shock, restraint, or refrigeration.

GLANDULAR ULCERATION IN THE ACTIVITY-DEPRIVATION RAT

Mechanisms which are implicated in the formation of glandular ulcers in other "stress" procedures (e.g. shock, refrigeration, or restraint) can also be applied to ulcerogenesis in animals subjected to the activity-deprivation procedure. As in other "stress" procedures, it is hypothesized that during the first few days of the restricted feeding schedule, levels of gastric acid in the stomach increase due to food deprivation (Glavin & Mikhail, 1976b). In an activity-deprivation situation, running can be considered

to be analogous to the sympathetic stimulation (Lamb, Ingram, Johnston, & Pitman, 1980) evoked during shock or refrigeration. Results of a study by Campbell and Lynch (1967) indicated that animals in an activity-deprivation experiment did not increase the overall number of activity periods but rather increased activity within a running session. This high activity within a brief time period probably evoked sympathetic activity which is similar to the sympathetic activity evoked during shock and/or restraint sessions. Therefore, as the animal begins to run more, gastric acid secretions might increase even more due to exaggerated parasympathetic functioning following cessation of running. Eventually glandular ulcers form.

Hara, Manabe, and Ogawa (1981) observed that one difference between animals which died and animals which survived the activity-deprivation schedule was the time of day when the animals ran. Survivors maintained normal nocturnal rhythms, whereas the victims switched from nocturnal to diurnal rhythms synchronized with the feeding time. Observations made during a pilot study indicated that activity animals were running prior to the feeding time. If an animal runs a normal amount during night hours, a "poststress" rest period may be created when the animal stops running, thus inducing

parasympathetic rebound. Therefore, instead of resting during the daylight hours (prior to feeding), the animal may run in an attempt to block the irritation of the stomach caused by the parasympathetic rebound.

Conflicting results exist, but it appears that if the severity of ulceration was reduced through decreasing gastric acid secretions, running activity was also reduced. When testing the antiulcerogenic effects of metiamide, Houser, Cash, and Van Hart (1975) observed that injections of metiamide given prior to the one hour feeding period significantly reduced ulceration. Running also tended to be suppressed at high dosages. In contrast, Pare, Glavin, and Vincent (1978) reported that injections of cimetidine, a potent gastric acid inhibitor, given following the one hour feeding period failed to reduce either the number or size of gastric lesions. Differences in daily running activity between animals receiving injections of cimetidine and those animals which received no injections also failed to be significantly different. If glandular ulcers are formed during the feeding period following high running activity, then the time of the injection of an antiulcerogenic drug is crucial and the results of Houser et al. (1975) and Pare et al. (1978) may be reconciled.

ROLE OF ADDITIONAL VARIABLES

Many additional variables have been manipulated to observe the effect on wheel running behavior. These variables include environmental temperature, time of day of feeding, reversed light cycles, and the effects of age. When any of these variables were manipulated, either speed of onset of exaggerated running and/or degree of ulcer severity was affected. For example, hypothermia was routinely observed in animals subjected to an activity-deprivation procedure (Bolles & Duncan, 1969; Hamilton, 1969; Pare, 1977). Upon first perusal, excessive running could be considered a self-defeating, thermoregulatory adaptive mechanism for the maintenance of body temperature. Hamilton (1969) reported that animals began to bar press for heat after several days of being on an activity-deprivation schedule and that running declined when the animals began bar pressing. Pare (1977) also suggested that animals ran in an attempt to maintain body temperature. However, when environmental temperature was increased to 31^{o} C and hyperthermia was exhibited, excessive running still occurred (Campbell & Lynch, 1967). Additionally, when subdermal temperatures were continuously monitored during the course of an activity-deprivation experiment, the beginning of a period of high running activity failed to

correlate with low body temperature. Results reported by Campbell and Lynch (1967) indicated that rats began to run when body temperature was at its highest and not at its lowest. Therefore, Campbell and Lynch (1967) concluded that subnormal body temperature was not a physiological stimulus for triggering excessive running.

Maintenance of an animal under a reversed light cycle or daytime feeding schedule tended to exacerbate ulcer development or to speed the occurrence of death (Hara et al., 1981).

Young rats less than 40 days old showed quicker onset of elevated running and more severe ulceration than did older rats (Pare & Houser, 1973). The differences in the speed of onset can probably be explained as a function of percentage of body weight lost in time; young rats are smaller than adult rats and body weight is more easily lost, which can both lead to a faster onset of elevated running and ulcer formation (Hara & Ogawa, 1983).

ROLE OF CENTRAL MECHANISMS

Increased turnover of norepinepherine (NE) in hypothalamic regions is highly correlated with both heightened activity and ulcer formation (Murphey & Nagy, 1979; Tsuda et al., 1981; Tsuda et al., 1982b). Tsuda et al. (1982b) reported that the rate of turnover of NE in

the hypothalmus of activity-deprivation animals showed a marked elevation when compared to the turnover rate of NE of food restricted animals housed in home cages. When animals remained in an activity-deprivation experiment for an extended period of time, a reduction in hypothalamic content of NE became evident (Tsuda et al., 1982b).

Considerable evidence suggests that the heightened activity induced by food deprivation alone is mediated by NE systems (Kety, 1970). Campbell and Fibiger (1971) reported that administration of d-amphetamine increased locomotor activity in a dose-dependent manner. By combining food deprivation with a constant dosage of d-amphetamine, behavioral arousal was further heightened. Because amphetamines are thought to act primarily on catecholamine (CA) systems (Groves & Rebec, 1976), Campbell and Fibiger (1971) suggested that the increased locomotor arousal resulting from food deprivation was also mediated by CA. Murphey and Nagey (1979) measured heightened activity of mice during food deprivation in a two hour shuttle cage test. When NE synthesis was blocked with injections of FLA-63, a dopamine-beta-hydroxylase inhibitor, the heightened activity previously observed by Murphey and Nagey (1979) was reduced to near baseline levels.

Lesions and chemical stimulation of both medial and lateral hypothalamic regions can lead to both the formation of ulcers and increased motor activity. Nobrega, Weiner, and Ossenkopp (1980) reported that animals subjected to medial and lateral hypothalamic lesions demonstrated severe ulceration of the glandular stomach. Postoperative motor activity was found to be positively correlated with the severity of gastric pathology. Lesions of the lateral hypothalmus (LH) led to acute gastric lesions whereas electrical stimulation of the thalmus did not have any effect on ulcer severity (Lindholm, Shumway, Grijalva, Schallert, & Ruppel, 1975). Additionally, when animals were subjected to preoperative dieting where weight was reduced to 80% of initial weight, the incidence of glandular ulceration following LH lesions was greatly reduced (Grijalva, Lindholm, Schallert, & Bicknell, 1976). Direct administration of NE onto LH regions also increased gastric secretions and promoted ulcerogenesis (Carmona & Slangen, 1973).

The amygdala is another brain region which has been implicated in both food deprivation increased arousal and in the production of glandular ulceration (Henke, 1980a, 1980b; Mabry & Campbell, 1975a, 1975b). The amygdala receives a large number of CA input, and it has been implicated experimentally as a primary structure for

mediating responses to stressful stimuli. In a review, Henke (1982) reported that visceral and nocioceptive information is transmitted (possibly through hypothalamic connections) to the centromedial amygdala and suggested that this region of the amygdala acts as a preventative response mechanism towards stress through determining the degree of aversiveness associated with peripheral pain sensations. Henke (1980a) also suggested that afferent pathways from the gut carry sensory visceral information to the amygdala.

Experimentally, lesions of the centromedial amygdala attentuate stomach pathology (Henke, 1980a) whereas lesions of the posteriolateral amygdala exacerbate stomach pathology (Henke, 1980b). Therefore, perhaps the amygdala, in conjunction with hypothalamic activity, mediates changes in the CNS in response to gastric irritation and induces the rat to run excessively in the activity wheel.

RELATIONSHIPS BETWEEN FOOD DEPRIVATION, GASTRIC ACIDITY, NOREPINEPHRINE TURNOVER, AND EXAGGERATED WHEEL RUNNING

Presently, it seems plausible that the degree of stomach emptiness during the course of the day could be the crucial factor which initially instigates high levels of wheel running. Furthermore, it is hypothesized that, through increased gastric secretions (originating from

food deprivation) and through the process of ulcerogenesis, feedback from the stomach to the brain triggers elevated rates of running. It is also hypothesized that once a critical level of activity is reached and percentage of body weight is lost, changes in the functioning of central mechanisms, such as increased turnover rate of hypothalamic NE (Murphey & Nagey, 1979), aid in maintaining the tenacity of wheel running behavior.

High NE turnover could enhance wheel running through further activation of CA systems or through further exacerbation of ulcer development (Carmona & Slangen, 1973). Heightened activation of CA systems is thought to lead to behavioral arousal through attenuation of habituation processes (Miezejeski, Lamon, Collier, & Hamilton, 1976; Murphey & Nagey, 1979). Murphey & Nagey (1979) measured heightened activity in mice as a function of 15 minute intervals. Results indicated that deprived animals and ad lib fed animals did not initially differ at the beginning of a test session; but as days of deprivation passed, deprived animals demonstrated much less of a within session decrease in activity than did ad lib fed animals. FLA-63, a NE synthesis blocker, eliminated any activity differences between experimental and control animals (Murphey & Nagey, 1979). Campbell

and Lynch (1967) reported that rats in an activity-deprivation experiment demonstrated greater increases of running within bursts of running but not a major increase in the total number of activity periods. Indeed, ability of an animal to survive the activity-deprivation procedure could depend on individual differences in response to "stressful stimuli" and concommitant changes in NE utilization. Weick, Ritter, and Ritter (1980) reported that the major differences in rats which survived and rats which died from a repeated restraint/tail shock procedure was the degree of elevation of catecholamine levels.

RELATIONSHIP BETWEEN INCREASED GASTRIC ACIDITY AND INCREASED WHEEL RUNNING

At least two plausible explanations exist to explain how increased secretions of gastric acid could lead to increased wheel running. Underlying both hypotheses is the idea that, as food deprivation continues within a day, the stomach walls come in closer contact with the gastric acids and this contact triggers the animal to run. It is hypothesized that, as days of food deprivation passed, both the production of gastric acid and the contraction of the gastric wall increased. In addition, introduction of "stressful stimuli" had an initial effect of disturbing blood circulation in the

gastric mucosa, leading to defective pyloric functioning and retention of gastric acid in the stomach. These occurences can lead to erosion of the mucosa and, together with vascular engorgement, can lead to hemorrhagic ulcers.

Many of the glandular ulcers observed in activity-deprivation animals appeared to lie on top of the folds of the glandular wall and along the muscularis mucosa (Manning, Wall, Montgomery, Simmons & Sessions, 1978). Location of ulcers suggests that ulceration occurred when the stomach was empty, thus contracted and in contact with the pool of gastric juices. Because ulceration tends to occur following high sympathetic activity and because animals appear to run more as length of time from the last feeding period inreases, it can be suggested that animals run more as the stomach walls come in closer contact with the highly acidic gastric secretions. Recall that ingestion of a non-nutritive bulk substance initially reduced running activity and that maintenance of an animal on a divided feeding schedule blocked both ulcer formation and excessive running (Hamilton, 1969; Tsuda et al., 1981). In both cases, the physical effect of food in the stomach could be the preventative variable which blocked ulcer formation and exaggerrated running. Presence of food in

the stomach could serve as a preventative measure through simply expanding the stomach, thus preventing and/or decreasing the amount of contact between the stomach walls and gastric juices.

If stomach discomfort due to the irritative effects of gastic acid leads to heightened activity, perhaps the animal runs in an attempt to block behaviorally the irritative effects of increased acid secretion. Recall that glandular ulceration can be prevented through sympathetic stimulation during the poststress rest period and that running can trigger high sympathetic activity.

PILOT STUDY

A pilot study was run in an attempt to replicate the "self-starvation behavior" of rats living in activity wheels. The pilot study was executed to allow direct observation of the self-starvation behavior of rats living in activity wheels and to ensure that the robust nature (Pare, 1980; Vincent, Pare, Isom, & Reeves, 1977) of the activity deprivation technique actually existed.

Results demonstrated that the activity-deprivation experiment was reliable and easily replicable. Figure 1 portrays the characteristic pattern of running and body weight lost which is normally viewed in an activity-deprivation experiment. The sharp peak in activity is routinely observed in an activity animal and

is indicative of the presence of glandular ulceration and the impending death of the animal (Pare & Houser, 1973). Although not systematically recorded, it appeared that animals were running little during the night and running more during the day. In animals which ran excessively, glandular ulcers were present.

Insert Figure 1 about here

SURVIVOR RATS

Curiously, some animals survive the activity-deprivation schedule and, in the present report, are referred to as "survivor rats". Initially, these animals demonstrate lower baseline running activity (approximately 200 to 700 revolutions per day) than do animals which do not survive the activity-deprivation schedule (approximately 2000 to 4000 revolutions per day). As days on the activity-deprivation schedule passed survivor rats gradually increased running activity until they were running from 3 to 10 times above baseline levels. Because baseline activity was lower for survivor rats at the start of the experiment, the overall level of running was still far below the level obtained by rats which did not survive the experiment. Survivor rats

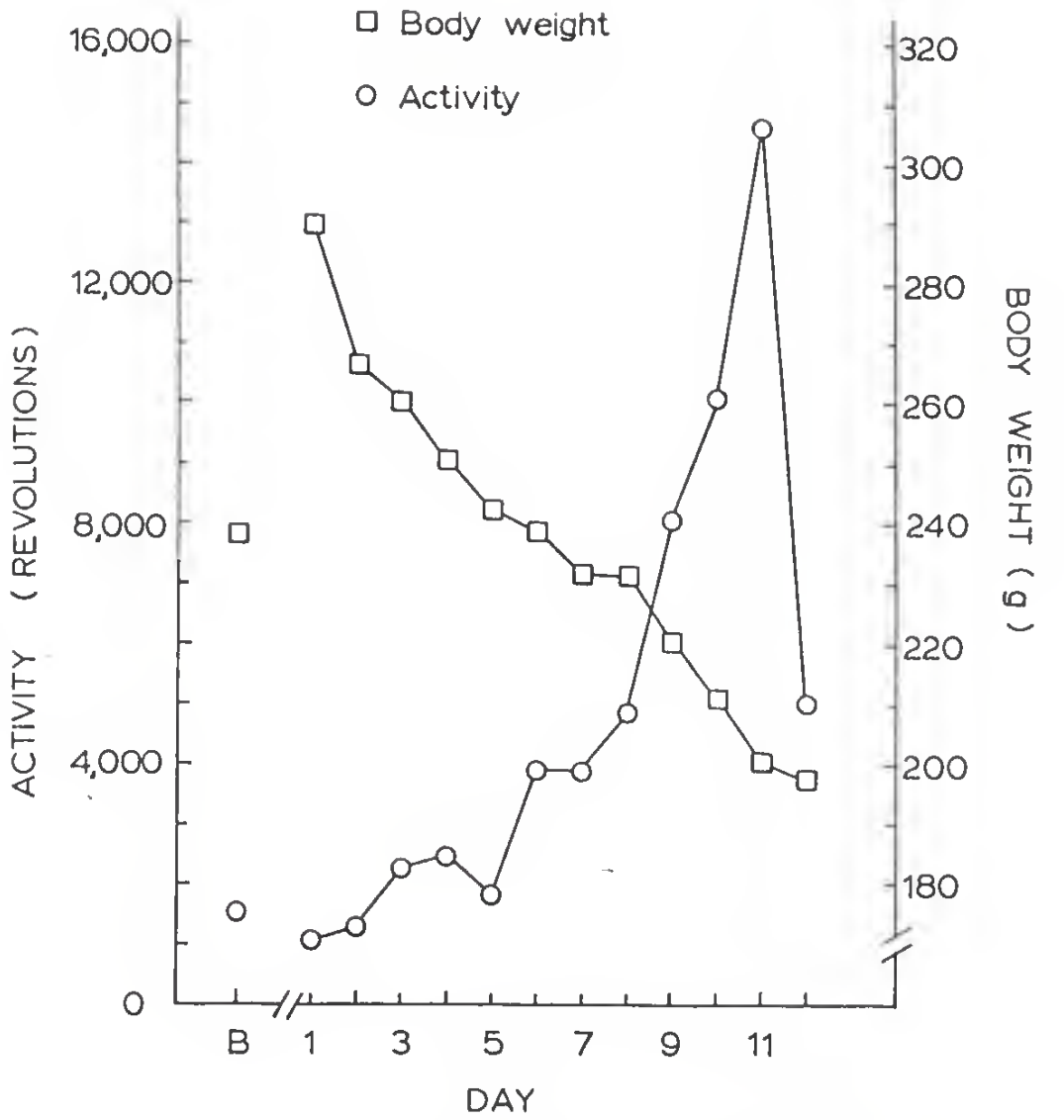

Figure 1. Daily course of changes in activity (in revolutions per day) and body weight (in grams) exhibited by a representative animal exposed to the activity-deprivation procedure.

exhibited no signs of glandular ulceration, were capable of stabilizing body weight, and showed no other ill effects.

Analysis of the characteristics of survivor rats may provide insight into understanding of why animals on the activity-deprivation schedule run excessively. For survivor rats, both overall running activity and loss of body weight per day were lower than for the animals which did not survive the experiment. Still, survivor rats drastically increased running. This increase in activity might be triggered by the irritative effects of increased gastric acid secretions which result from food deprivation. Perhaps these rats survive because body weight declined more gradually. If a critical interaction between increasing activity and decreasing body weight was necessary to trigger excessive activity, perhaps survivor rats survive because this critical interaction never occurs. Thus, survivor rats are never thrown into a viscious circle of high energy expenditure in times of severe deprivation.

PURPOSE

The purpose of the present experiments was to investigate the effects of pre-adaptation to a restricted feeding schedule and the effects of ulcer formation on the instigation and maintenance of excessive wheel

running in food restricted animals. It was hypothesized that an aversive condition of increased quantities of gastric acid in an empty stomach may exist and may serve as an impetus for exaggerated wheel running. Previous research suggested that animals tended to run more as the stomach became more empty over a 24 hour period. For example, animals which demonstrated high rates of running activity switched from a nocturnal to a diurnal activity schedule that was synchronized with the daily feeding period. Animals that did not run excessively maintained a nocturnal rhythm unrelated to the onset of feeding times (Hara et al., 1981). Also, animals run much less if fed on an ad lib schedule (Hall et al., 1953; Moskowitz, 1959; Glavin & Mikhail, 1975), fed with non-nutritive bulk (Hamilton, 1969), or fed in two, divided one-half hour periods (Tsuda et al., 1981). Taken together, the above studies suggest that, as the stomach becomes empty, the animal runs more.

Pare and Houser (1973), along with other investigators, have termed the combination of free access to a running wheel plus a 1 hour/day feeding schedule as an "activity-stress" paradigm. "Stress" was defined as food deprivation and loss of body weight. In the previous discussions and in the ensuing studies, this experimental procedure was simply referred to in

descriptive terms as the activity-deprivation procedure. This was done in an attempt to avoid the negative and ambiguous connotations associated with the word "stress". Studies previously reported in the "stress" literature indicated that food deprivation was a necessary component, rather than the source of the stress, to any experimental procedure designed to produce gastric lesions or "stress ulcers." Stress and the development of glandular ulcers were produced through superimposing an aversive procedure such as restraint, shock, or refrigeration on top of the food deprivation (Glavin & Mikhail, 1975, 1976b; Pare, 1980). Therefore, in an activity-deprivation situation, it can be suggested that the sympathetic activity induced by wheel running, rather than the food deprivation, is the stressor which promotes the development of glandular lesions. In the following studies, one consequence of a restricted feeding schedule, the condition of a relatively empty stomach, is examined through pre-adaptation to a restricted feeding schedule and the administration of an anti-ulcerogenic drug during the course of the activity-deprivation experiment.

EXPERIMENT 1

Experiment 1 was designed to clarify the severity of both the behavioral and physiological consequences of an

activity-deprivation procedure as a function of the number of days of a rat's prior experience on a restricted feeding schedule. As discussed earlier, animals pre-adapted to a restricted feeding schedule for 7, 14, or 15 days (Glavin, 1978; Pare et al., 1978) failed to show lower levels of running activity, failed to lose less body weight, and did not show a reduction in glandular ulceration, when compared to animals which did not have previous experience on a restricted feeding schedule. In contrast, other investigators (Seiser & Kackinnon, 1976) reported that the habituation of an animal to a restricted feeding schedule for 33 days prior to its entrance into an activity wheel increased the amount of food consumed each day, as well as decreased running activity, body weight loss, and the incidence of stomach lesions. Combined, the results of the above studies suggest that the greater the prior habituaton to a restricted feeding schedule, the greater the possibility that a rat will run only moderate amounts, will fail to develop glandular lesions, and will survive the duration of the experiment.

Leiveille and O'Hea (1967) reported that it takes approximately 30 days of experience on a restricted feeding schedule for a rat living in a home cage to ingest enough food to maintain a stable body weight, and

to show energy conservation and a more efficient metabolism than animals on an ad libitum diet. Therefore, pre-adaptation to a restricted feeding schedule for periods of time less than 30 days might not be sufficient for the animals to stabilize both food intake and body weight before entering the activity wheels. Pre-adaptation to a restricted feeding schedule for periods of time greater than 30 days might be sufficient to enable the animals to enter the activity wheels with both daily food intake and body weight stabilized. Also, the increased secretion of gastric acid brought on by a restricted feeding schedule is minimized through prior adaptation to a 1 hour per day feeding schedule (Glavin & Mikhail, 1976b). It can be suggested that the 33 day pre-adapted animals in the Seiser and Kackinnon study (1976) survived activity-deprivation situations for reasons similar to why ad libitum feeding animals survived. Both ad libitum feeding animals and the 33 day pre-adapted animals may not run excessively because both groups of animals ingest enough food to maintain a relatively stable body weight and secrete a minimal amount of gastric acid into the stomach.

It was hypothesized that, as rats become more habituated to a restricted feeding schedule, the daily

amount of food consumed would increase, the daily amount of body weight loss would decrease, and the daily amount of running activity would decrease. Also, the overall incidence of gastric erosions should decrease in animals that are completely habituated to the restriced feeding schedule. If the length of prior experience on a 1 hour feeding schedule is not sufficient to stabilize both food intake and body weight loss, the animals may begin to run sooner and to die faster than animals which were not subjected to food deprivation before entering the running wheels. Ultimately, any potentiating effects that a restricted feeding schedule has on wheel running and ulcer formation should be minimized through extending the amount of time of pre-adaptation on a restricted feeding schedule.

METHOD

Subjects. Fifty-six Holtzman female albino rats, 40 days old and weighing between 140 and 160 grams, were housed in group cages until the beginning of each baseline period. At the beginning of each baseline period animals were approximately 60 to 100 days old and weighed between 200 and 300 grams. Temperature and relative humidity in the rooms where activity and control cages were housed were recorded daily. The light cycle for both rooms was a normal light/dark cycle with lights going on at 7:00

A.M. and turning off at 7:00 P.M.

Apparatus. Seven Wahmann activity wheels of standard size attached to a small living cage (25 X 15 X 12.5 cm) were used. A counter attached to each wheel recorded the number of full revolutions made by the wheel. In addition, a set of microswitches recorded the number of full revolutions made by each wheel during three different time periods. For baseline measurements, these time periods were: 7:30 PM-3:10 AM, 3:10 AM-10:50 AM, and 10:50 AM-6:30 PM. For the experiment proper, these time periods were: 8:30 PM-3:50 AM, 3:50 AM-11:10 AM, 11:10 AM-6:30 PM.

Procedure. All animals were adapted to activity cages for a period of 5 days. During the adaptation period, each animal spent 24 hours/day in the activity cage with free access to the running wheel; Purina Lab Chow and water were available ad libitum. Animals living in the activity wheels were weighed daily and baseline measures of food intake (in grams), water intake (in grams), and activity (in revolutions) were recorded daily between 6:30 PM and 7:30 PM. At the end of the 5 day baseline period, animals were returned to individual home cages and provided with food and water ad libitum. Due to the small number of running wheels, only 7 animals were run in each baseline group. A total of 8 baseline groups

were run over successive 5 day periods.

Following baseline measurements, all 56 animals were divided into 4 experimental and 4 control groups which were matched for mean baseline activity rates. Experimental Groups 1, 2, 3, and 4, had either 0, 15, 25, or 35 days, respectively, of pre-adaptation to a restricted feeding schedule prior to re-entering the activity wheels. Control Groups 5, 6, 7, and 8 had identical pre-adaptation schedules as the matched experimental groups but were housed in home cages in the animal room and never re-entered the activity wheels. Ten days after the last baseline group was run, Group 1 re-entered the activiy wheels for 18 days. Groups 2, 3, and 4 re-entered the activity wheels in the successive 18 day periods. For all experimental groups, access to the running wheel was blocked for approximately 2 hours, from 6:30 PM-8:30 PM, on a daily basis. Animals were weighed between 6:30 PM-7:00 PM, left undisturbed from 7:00 PM-7:30 PM, and fed between 7:30 PM-8:30 PM. At the end of each feeding hour, spillage and remaining food was collected and weighed to the nearest .1 gram. Water intake was also measured at the cessation of the feeding period.

For all experimental groups, animals were sacrificed with an overdose of sodium pentobarbital when the

following signs were observed: a sharp increase in running which peaked and then quickly decreased and was accompanied by a sharp reduction in the amount of food consumed per day. A subjective evaluation of the physical appearance of the rat was also utilized to determine the time of sacrifice. Whenever an animal became hunched, listless, and displayed piloerection, the animal was immediately sacrificed. Together these signs indicated the approaching death of the animal. If animals survived the activity-deprivation schedule, they were sacrificed at the end of the 18 day experimental period. All animals were blocked from the running wheel for approximately 2 hours before sacrifice. Whenever an experimental animal was sacrificed, its control was also overdosed with pentobarbital.

After an animal was sacrificed, the stomach was removed and opened by cutting along the greater curvature, washed thoroughly with saline, and fixed in a 10 percent Formalin solution. The number, location, and length (in millimeters) of the ulcers were recorded. Ulceration was measured to the nearest .5 mm and rated according to the method of Goldstein and Wozniak (1979) where: a lesion less than 1 mm in its longest dimension was given a value of .5; from 1-2 mm = 1.5; 2-3 mm = 2.5; and so on. These values were summed for the stomach to

yield a score which represented an index of the severity of erosions. To ensure consistency in the scoring of the stomachs, all stomachs were allowed to remain in the formalin solution for at least three weeks prior to scoring, and all stomachs were rated on the same day at approximately the same time period. To validate the erosion scores judged by the rater, a second rater randomly selected stomachs and scored the gastric erosions.

RESULTS

Behavioral

Results from Experiment 1 indicated that the experience of pre-adaptation to a restricted feeding schedule affected subsequent performance in the running wheel. As viewed in Table 1, all groups were initially well-matched on baseline running rates; a between group analysis of variance indicated that there were no significant differences between any of the groups in the amount of running done during each time period while maintained on ad libitum feeding. Additionally, when food and water were provided ad libitum during baseline, animals in each groups ran the most during the 8:30 PM to 3:50 AM time period and ran the least during the daylight hours of 11:10 AM to 6:30 PM.

Table 2 shows that the greater time of

pre-adaptation experience the more likely an animal was to survive for the duration of the 18 day experiemtnal period. Animals with intermediate pre-adaptation experience of 15 and 25 days were sacrificed within a fewer number of days than either the 0 or 35 day pre-adaptation groups.

Insert Table 1 and 2 about here

On Day 1 of the activity-deprivation schedule (see Figure 2), there were no significant differences between pre-adaptation groups in the amount of running during each time period. Animals with pre-adaptation experience tended to run above baseline values previously recorded during ad libitum feeding and run more than animals without prior pre-adaptation experience during the 11:10 AM to 6:30 PM period. Running during the remaining two time periods did not seem to be affected by pre-adaptation experience.

Figure 3 illustrates that, for the first five days of the experimental schedule, animals pre-adapted to the restricted feeding schedule ran above baseline values recorded for the 11:10 AM to 6:30 PM period, while running during the other two time periods was close to the running values recorded during ad libitum feeding.

Table 1

Mean Baseline Activity (in revolutions per day) of Animals Subsequently Exposed to Different Pre-adaptation Experience

Condition	n	Time Period		
		8:30 PM.- 3:50 AM.	3:50 AM.- 11:10 AM.	11:10 AM.- 6:30 PM.
0 Day	7	603	276	130
15 Day	7	622	312	113
25 Day	7	733	331	231
35 Day	7	719	310	242

Table 2

Mean Number of Days to Peak Activity for Victims and Survivors with Different Pre-adaptation Experience

		Days To Peak	
Group	n	Mean	S.E.M
0 Day			
Victims	5	12.4	0.67
Survivors	2	18.0	--
15 Day			
Victims	3	5.3	1.51
Survivors	4	18.0	--
25 Day			
Victims	2	6.5	0.35
Survivors	5	18.0	--
35 Day			
Victims	1	13.0	--
Survivors	6	18.0	--

Thus, the major increases in running during the first 5 days occurred during the time period which was furthest away from the time in which the animals were previously fed. Animals not pre-adapted to the restricted feeding schedule did not show as great an increase in running during the 11:10 AM to 6:30 PM period over the first five days.

Insert Figures 2 and 3 about here

On peak day (see Figure 4), all exerimental groups drastically increased running between 11:10 AM and 6:30 PM, while the amount of running during the rest of the day was similar to baseline values. A between group anaylsis for running on peak day was not significant for any of the 3 time periods even though animals previously adapted to the restricted feeding schedule tended to run greater amounts during the daylight period. A repeated analysis of variance for percent change scores in running during the 11:10 AM - 6:30 PM period for baseline, Day 1, and peak day, was significant for the 0 Day group ($F(2,12) = 7.73$, $p < .01$) and for the 35 Day group ($F(2,12) = 13.35$, $p < .001$). Only a general trend towards significance was observed for increased running on peak day in the 15 Day and 25 Day groups ($.05 < p < .15$).

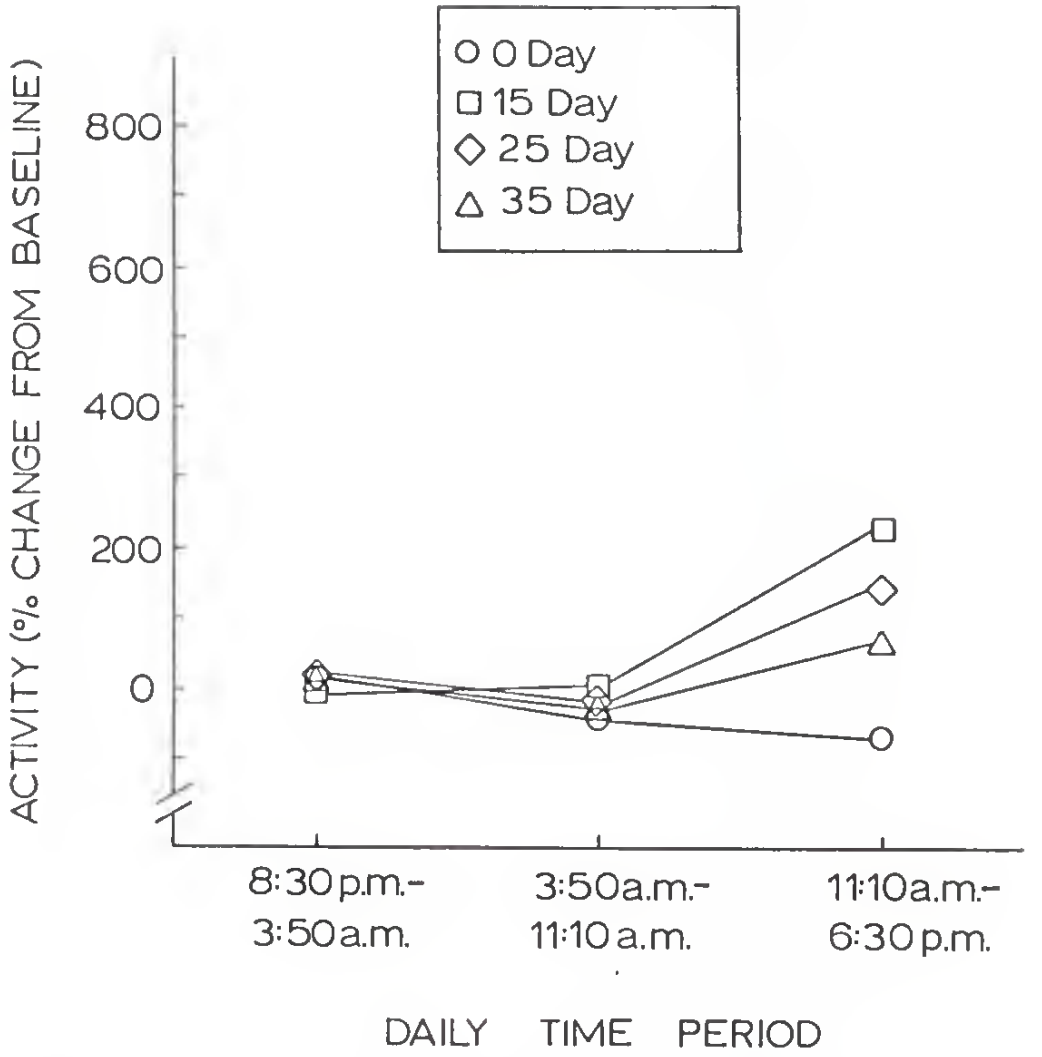

Figure 2. Percent change from baseline activity recorded during three time periods on day 1 for animals exposed to different amounts of pre-adaptation on a restricted feeding schedule.

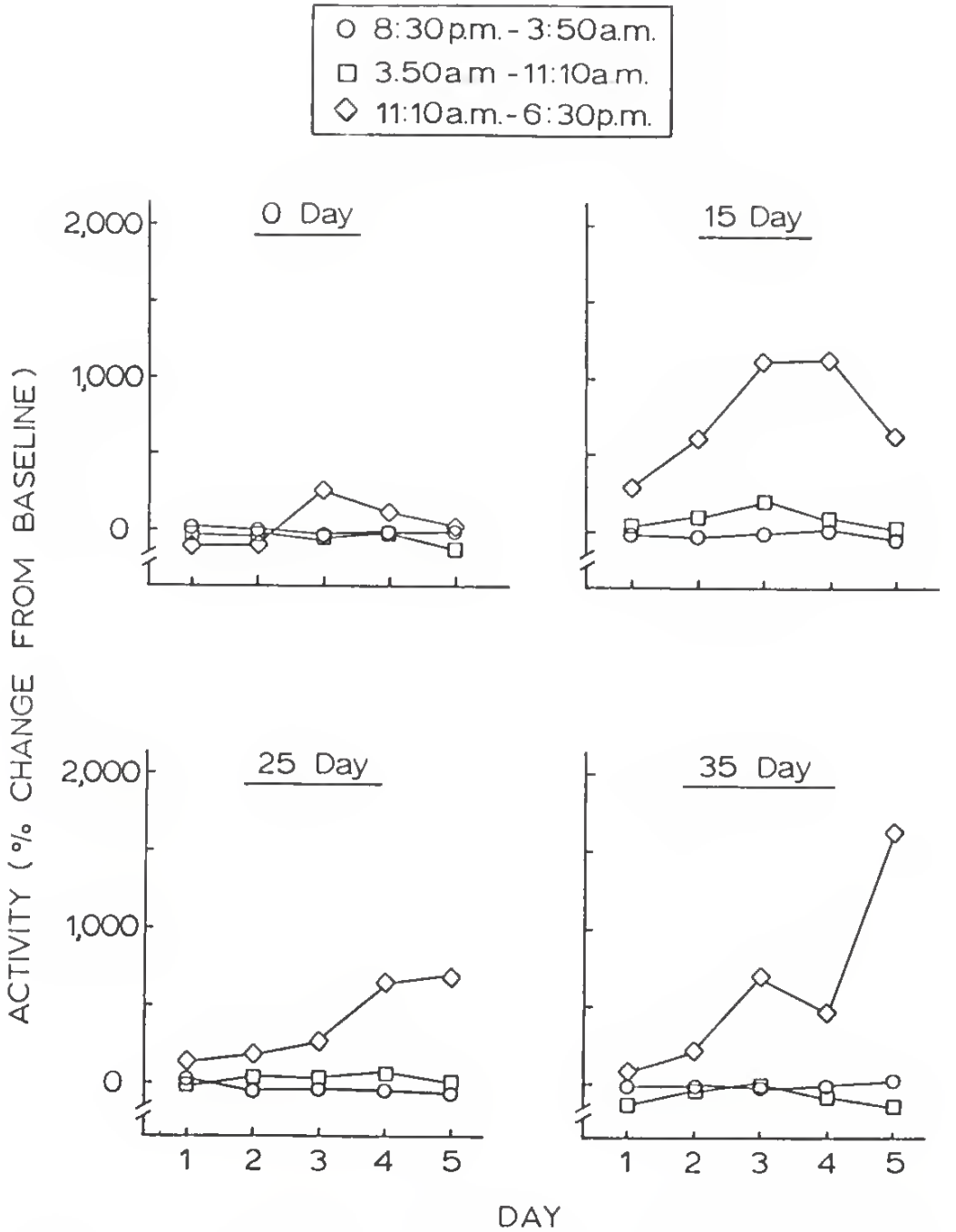

Figure 3. Percent change from baseline activity recorded during three time periods over the first five days for animals pre-adapted to a restricted feeding schedule for a different number of days.

Insert Figure 4 about here

Both a between group analysis and a repeated measures analysis for amount of food consumed, amount of water drunk, and amount of body weight lost for each group during baseline, Day 1, and peak day indicated that there were no significant differences between activity animals and home cage controls on any day. Across the days of the experiment most of the groups increased their food intake. For the pre-adaptation groups there were no significant differences in amount of food eaten in home cages on the last day of the pre-adaptation schedule and the amount of food eaten on Day 1 of the testing period (see Table 3). No significant differences in water intake were observed between activity animals and home cage animals of any pre-adaptation group across the days of the experiment. Animals without prior pre-adaptation experience drank slightly less amounts than did animals previously adapted to the restricted feeding schedule (see Table 4). Over the course of the experiment both activity animals and home cage controls lost weight, with the activity animals showing slightly greater drops in weight (see Table 5).

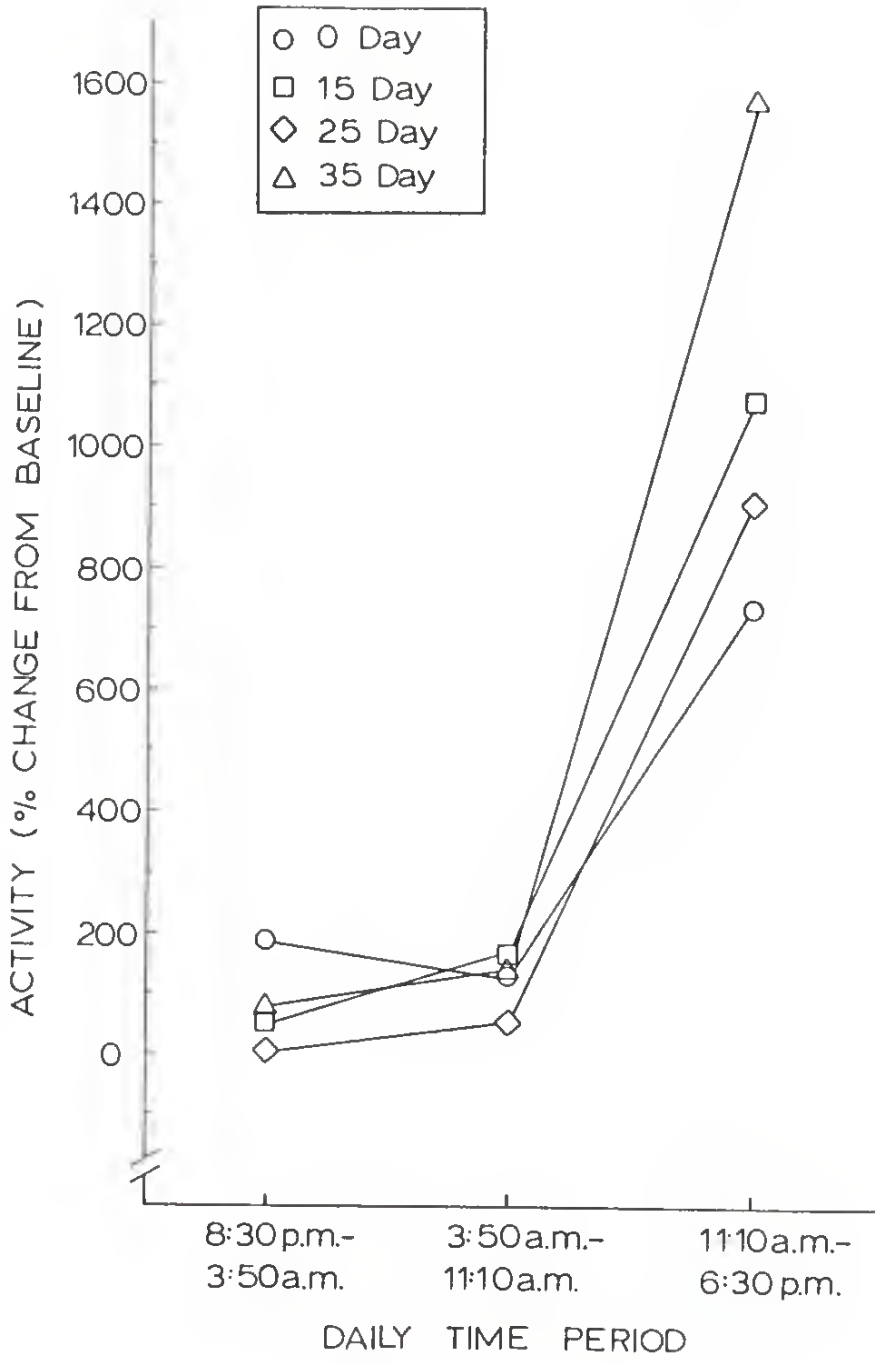

Figure 4. Percent change from baseline activity on peak day recorded during three daily time periods for animals exposed to different amounts of pre-adaptation to a restricted feeding schedule.

Insert Tables 3, 4, and 5 about here

Behavioral Observations. The behaviors that animals on an activity-deprivation schedule exhibited over the 18 day testing period were curious and as of now, evade explanation. Most notable were the rats' running and feeding behaviors. As previously viewed during a pilot study, the tenacity of the wheel running was rather extraordinary. For example, occasionally an animal would rapidly regress into a weakened state within a few hours and display difficulty in walking and standing; but the animal would still enter the activity wheel and begin to run (albeit less vigorously). The running behavior viewed in animals several days prior to peak day appeared to have a higher degree of intensity associated with it than the more relaxed running observed during ad libitum conditions. Also notable in the running activity of animals was the vast array of individual differences in the overall amount of running and number of days in which an animal could endure the heightened activity. For some animals, approximately 2000 revolutions per day was sufficient to cause ulceration, whereas other animals would run up to 16,000 revolutions per day and exhibit a similar degree of

Table 3

Mean Amount of Food Consumed by Animals with Different Pre-adaptation Experience

	Period			
Group	Ad Libitum	Last Day	Day 1	Peak
Activity				
0 Day	12.5	--	3.8	6.4
15 Day	12.4	11.7	11.1	12.1
25 Day	13.6	13.1	10.9	12.6
35 Day	15.0	12.5	12.1	15.4
Home Cage				
0 Day	13.2	--	6.4	11.6
15 Day	13.3	10.9	10.7	12.4
25 Day	13.2	13.5	13.8	11.3
35 Day	10.5	12.5	13.7	13.9

Note: $n = 7$ for each group

Table 4

Mean Amount of Water Consumed by Animals with Different Pre-adaptation Experience

	Period			
Group	Baseline	Last Day	Day 1	Peak
Activity				
0 Day	34.7	--	30.7	24.7
15 Day	49.9	32.5	42.0	43.9
25 Day	29.1	35.6	35.4	35.0
35 Day	38.7	37.3	21.2	23.1
Home Cage				
0 Day	42.5	--	27.7	23.2
15 Day	29.4	54.6	29.7	31.6
25 Day	36.3	36.5	29.0	36.4
35 Day	39.4	37.2	35.5	37.9

Note: $n = 7$ for each group

Table 5

Mean Body Weight of Animals with Different Pre-adaptation Experience

	Period			
Group	Baseline	Last Day	Day 1	Peak
Activity				
0 Day	251	-	289	198
15 Day	255	240	239	203
25 Day	250	236	234	210
35 Day	262	255	245	220
Home Cage				
0 Day	259	-	299	248
15 Day	244	233	231	223
25 Day	244	251	249	245
35 Day	254	232	224	227

Note: n = 7 for each group

ulceration to the 2000 per day runner.

Length of time in which increased running could be physiologically supported also varied within animals. Some animals progressively increased running over a period of days with only a slight deterioration in appearance; and other animals appeared to peak within a day and then rapidly decline in appearance. Finally, a difference in the pattern of running observed during testing but not during any baseline period, was the sporadic but complete discontinuation of running for a day to several days by animals in the 0 Day and 15 Day groups.

Pre and post feeding behavior also appeared to change over the course of the 18 day period for activity animals. During ad libitum feeding, some animals would paw at the closed door to the running wheel when being weighed. During the food restriction period the incidence of pawing at the door seemed to increase in both frequency and intensity. Activity animals also displayed occasional gnawing at the cage bars. In control animals, the only adjunctive behavior observed was gnawing at the bars by the majority of all home-caged food restricted animals. When food was delivered to the activity rats at the 1 hour feeding period, those animals exhibiting daily increases in running appeared to be

hyperactive and agitated. Instead of directly settling down to eating (as they previously had done), the activity rats would frantically toss all the food to one corner of the cage, then nibble for a few seconds, and begin to toss the food around again. By the end of the feeding hour, the hyperactive animals had consumed approximately the same amount of food as they usually did during the one hour.

Both activity animals and control animals appeared willing to ingest non-food substances. For example, the activty animals would nibble voraciously at the bedding if a piece of it could be reached. When the 25 Day activity and control groups were sacrificed, the cages were placed on paper towels and the majority of the animals consumed the paper towels and wadded balls of paper were observed in the empty stomach.

Activity animals which were sacrificed along the course of the 18 day experimental period displayed some unique patterns of behavior not previously viewed in those animals. On the day that the activity animals met the sacrifice criterion, animals appeared somewhat weakened but were more likely to cling stubbornly to any food held in the mouth. Additionally, on the day designated for sacrifice, an animal was more likely to attempt an escape from the open cage door and was more

likely to bite and cling to the experimentor's glove by its teeth.

Glandular Ulceration

Results indicated that animals pre-adapted to a restricted feeding schedule exhibited fewer number of ulcers (see Figure 5). Statistical tests performed on the number of ulcers between the 0 Day group and the 3 pre-adaptation groups demonstrated that only the 15 day group had significantly fewer ulcers (t (12) = 2.65, $p < .05$). In the 25 and 35 Day groups the difference in the number of ulcers when compared to the 0 Day group approached statistical significance ($.05 < p < .10$). Figure 6 illustrates that all pre-adaptation groups had smaller ulcers than the group not pre-adapted but the difference in the length of ulcers only approached statistical significance ($.05 < p < .15$).

Insert Figures 5 and 6 about here

In activity animals, severe ulceration was observed and usually occured along the folds of the glandular stomach (see Figure 7). Less severe ulceration was observed to occur along the areas were the folds had been previously but appeared to be worn down (see Figure 8).

None of the animals in the food restricted home cage

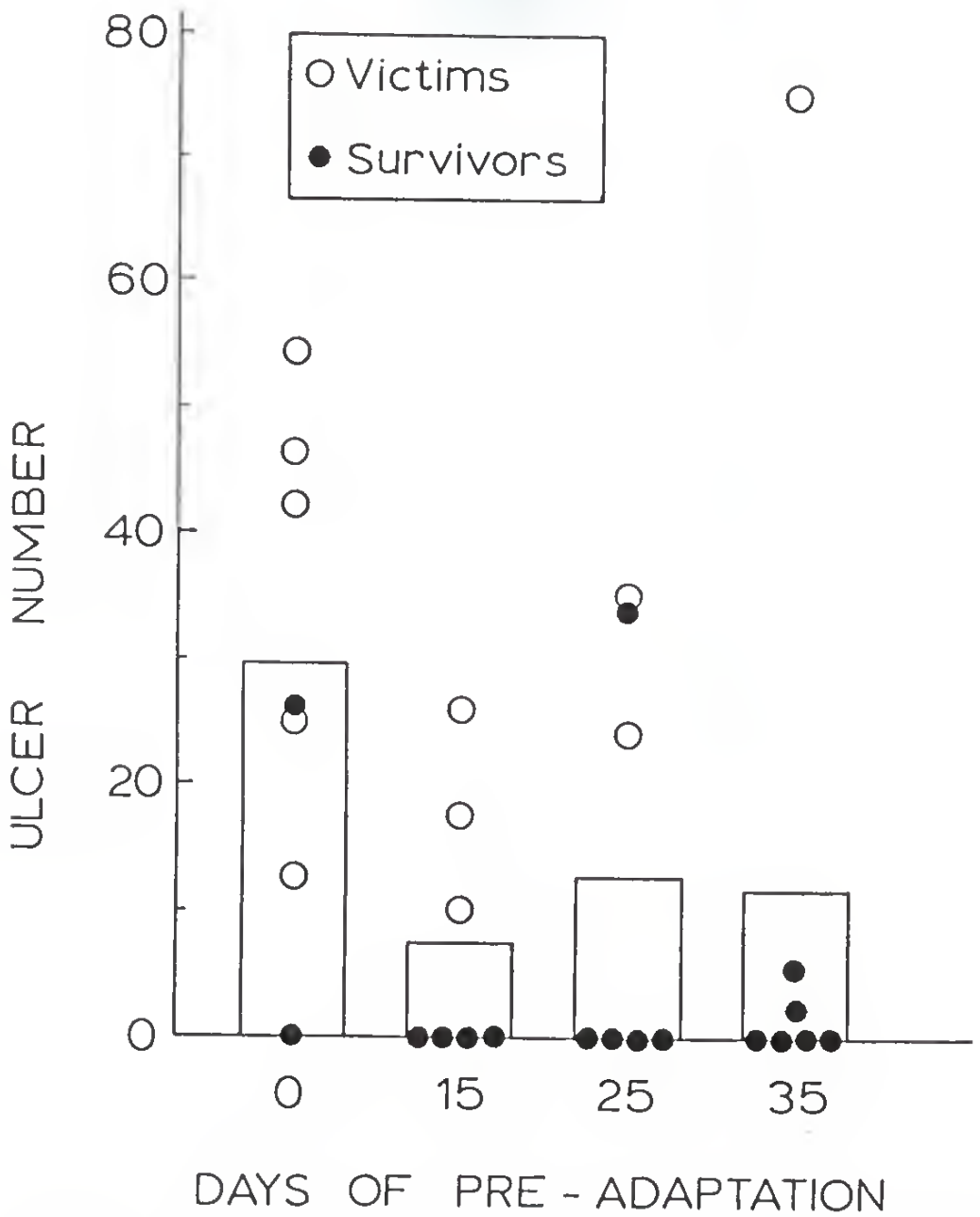

Figure 5. Mean number of glandular ulcers for victims and survivors of animals exposed to different amounts of pre-adaptation to a restricted feeding schedule.

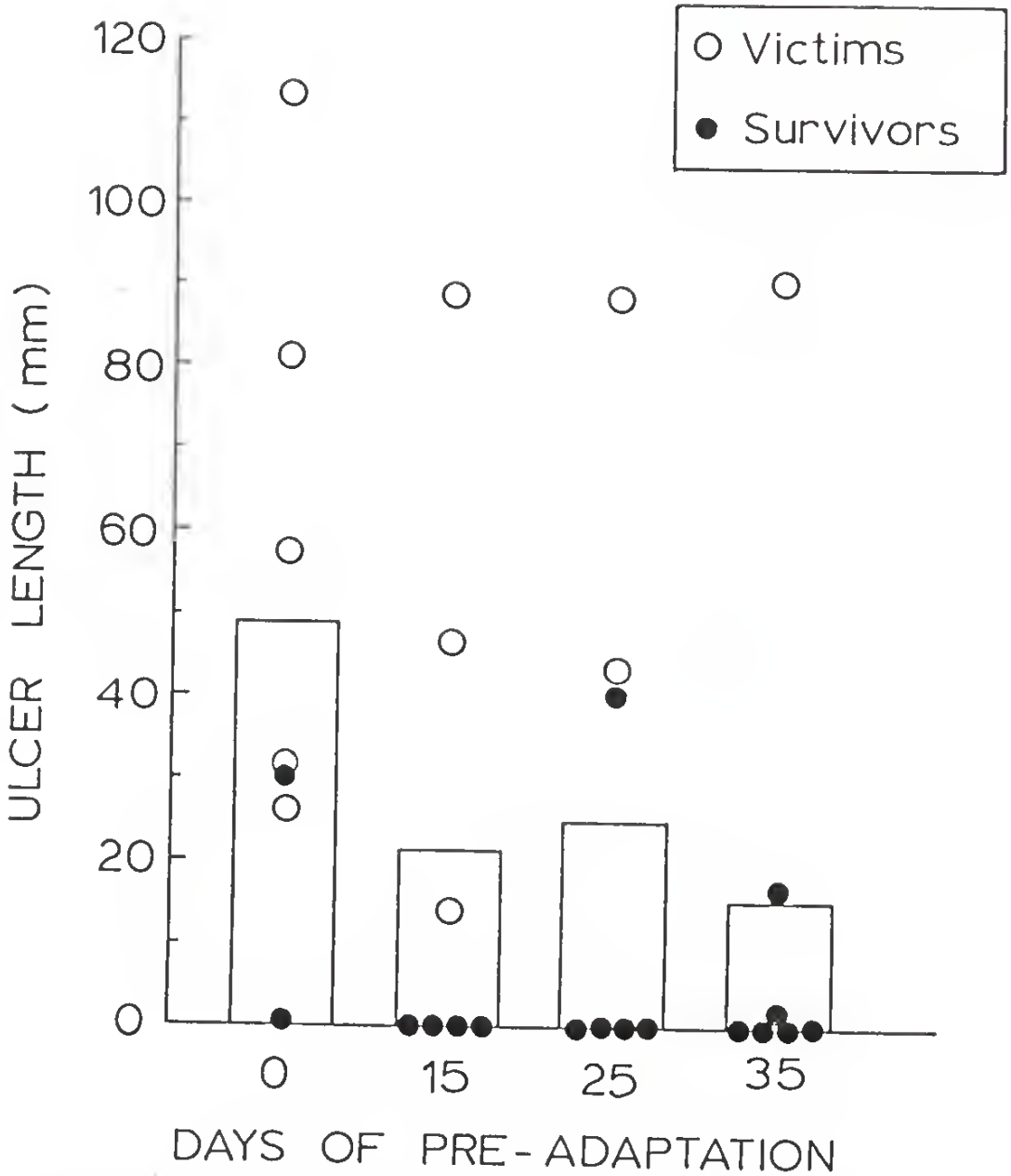

Figure 6. Mean glandular ulcer score (in mm) for victims and survivors of animals exposed to different amounts of pre-adaptation to a restricted feeding schedule.

groups had ulcers in the glandular stomach, although the folds were slightly smoothed over (see Figure 9). Occassionally, in both the activity and the home cage animals, slight ulceration of the rumen was observed but not quantified due to the scarcity of incidence and the apparently random occurence in either the activity or the control animals.

Insert Figures 7, 8, and 9 about here

Gross Pathology Observations. Both activity and home cage animals which had experienced pre-adaptation to a restricted feeding schedule had smoother stomachs with less folds present than did animals not experiencing pre-adaptation. Additionally, some of the stomachs in the pre-adaptation groups appeared to have thinner, and less elastic stomach walls. When autopsied only 2 rats of the 25 Day control group, 1 rat of the 25 day experimental group, 3 rats of the 35 Day control group, and 4 rats of the 35 Day experimental group had residual food left in the stomach.

In all the animals of Experiment 1, no visible fat stores were present. Both control and experimental animals also tended to have livers which were bleached white along the fringes of the posterior lobe. There were

Figure 7. Representative stomach of an activity-deprivation animal with severe glandular ulceration.

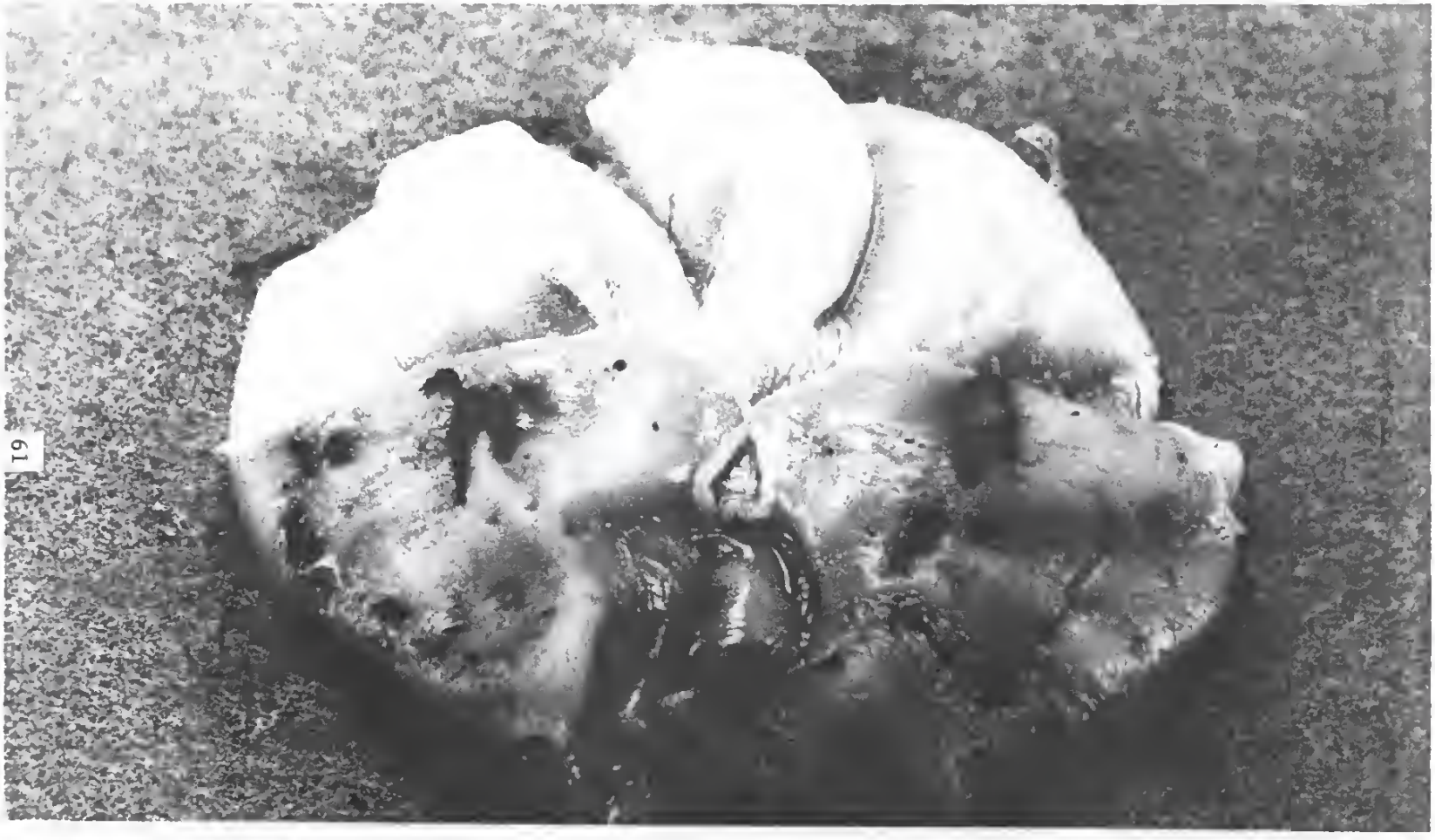

Figure 8. Representative stomach of an activity-deprivation animal with mild glandular ulceration.

Figure 9. Representative stomach of a home-cage animal on a restricted feeding schedule without glandular ulceration.

also livers which had a few darkened blotches on the core and along the fringes of the posterior lobes.

The ulcerated activity victims of Experiment 1 had intestines which were very dark along virtually the entire length of the intestinal tract. Activity animals also had rather large adrenal glands, which were aproximately the size of a half peanut. Both the liver and the spleen of activity animals were somewhat smaller than the liver and spleen of home-caged animals.

DISCUSSION

Behavioral

Analysis of the results from Experiment 1 indicated that maintenance on a restricted feeding schedule does not block excessive wheel running but does induce a change in the pattern of daily running, as well as influencing survival rate and the ease in which glandular ulcers form. Regardless of the extent of prior adaptation to a restricted feeding schedule, all animals exhibited large increases in running on peak day during the time period before the feeding hour (third time period); for the remaining 2 time periods, running was close to baseline values. In addition, animals with pre-adaptation experience lost comparable amounts of weight but had less ulceration and were more likely to survive for the duration of the 18 day experimental

period than animals without pre-adaptation experience. The observed increase in running during the third time period appeared to be an outcome dependent on food deprivation but what appeared to determine the demise of the animal was the interactive effects of high activity with the physiological state of the rat.

Both the subjective state and the physiological state of the stomach was postulated to account for the dramatic increases in daytime running exhibited by animals on a restricted feeding schedule. Richter (1927) reported that, in ad libitum fed animals, an increase in activity could be observed just prior to the initiation of feeding; he concluded that "hunger contractions" stimulated the animals into activity. The data presented from Experiment 1 support the hypothesis that hunger contractions and the degree of irritation of the stomach, influenced by the absence of bulk and the process of ulcerogenesis, initially trigger the animal to begin to run at a time in which it normally does not.

All animals with previous experience on a restricted feeding schedule exhibited a greater change from baseline running on Day 1 during the third time period than did animals which did not have previous experience on a restricted feeding schedule. Animals which had no prior experience with food restriction before entering the

activity wheels were probably fairly satiated on Day 1 and running scores were not affected, if the stomach had a moderate amount of food and degree of comfort. Groups with either 15 days or 25 days of pre-adaptation experience might have had relatively empty stomachs on Day 1 and may have been induced to run during the daylight periods as the stomach became emptier over time from the last feeding session. For the animals with 35 days of pre-adaptation, Day 1 activity rates might not be as affected by the condition of the stomach due to habituation to the feeding schedule.

Running rates during the first five days also support the notion that the lack of bulk in the stomach may influence the animal to run. Animals pre-adapted to the restricted feeding schedule ran more during the third time period over the first five days of the experiment than did the 0 Day group which ran close to baseline values on the first five days.

Contrary to previous discussions (Routtenberg, 1968; Routtenberg & Kuznesof, 1967), the decrements in food intake usually observed in an activity-deprivation experiment can be inferred to result from unfamilarity with the feeding schedule as opposed to an exhibition of self-starvation; all animals tended to increase food intake over the course of the experiment. Additionally,

no significant differences in amount of food consumed by activity animals and the food yoked, home-cage animals were observed for any pre-adaptation group. The food consumption data indicated that activity animals in the 0 Day group gradually increased their food intake in a manner similar to the home-cage controls over the course of the experiment, while amount of food intake for both activity and control rats remained below the amount ingested by pre-adapted groups. Both activity and home-cage animals on pre-adaptation schedules retained approximately normal amounts of food consumed during the testing period and probably consumed as much food as possible in the allotted feeding hour.

Glandular Ulceration

Results indicated that any amount of pre-adaptation was sufficient to reduce ulceration but only survival rate was affected in a progressive manner. Glavin and Mikhail (1976b) reported that if the initial increase in gastric acidity induced by food deprivation was minimized, subsequent application of a "stressor" would lead to less ulceration. In an activity-deprivation experiment, prior habituation to the feeding schedule may also reduce gastric acid hypersecretion brought on by food deprivation and result in less ulceration after experiencing the high sympathetic stimulation of running.

The greater increases in daytime running exhibited by pre-adaptation groups on peak day, in combination with the progressively greater survival rate and lower indices of ulcer severity, suggest that high levels of activity were not killing the animals but rather were interacting with the physiological consequences of food deprivation, as well as facilitating ulcer formation and eventually resulting in the death of the animal. The mean days to peak for the victims of different pre-adaptaton groups also suggests that survival may be influenced by the current bodily state or the condition of the stomach. The victims of both the 0 and the 35 pre-adaptation groups were sacrificed in a mean of 12 to 13 days, while the victims of the 15 and 25 Day pre-adaptation groups were sacrificed in a mean of 5 to 6 days.

For the 0 Day group, it might have taken approximately 12 days for the normal residual bulk maintained in the stomach during ad libitum feeding to be depleted and leave the stomach vulnerable to the effects of the pathological agents of ulcerogenesis. In the 35 Day pre-adapted group, the prior habituation to the feeding schedule might have been sufficient to decrease the hypersecretion of gastric acidity induced by food restriction; therefore, the high activity could be physiologically supported and could account for the high

survival rate in the 35 Day group. The 15 and 25 Day pre-adapted groups might not have been completely habituated to the restricted feeding schedule and were thus rendered more vulnerable to the effects of high activity and succumb more easily to the harsh rigor of excessive activity during food restriction. In the 15 and 25 Day pre-adapted groups, the stomach was probably relatively depleted of residual bulk and possibly still hyperacidic as a result of lack of complete habituation to the restricted feeding schedule. Therefore, the high daytime activity might have led to a quicker formation of ulcers, subsequent hemorrhaging, and a quicker demise in animals not completely adapted to the restricted feeding schedule.

The fact that the majority of the 35 Day animals survived the longest suggests that the irritative process of ulcerogenesis may not be the only factor mediating increases in daylight running. Unless a threshold of irritation exists which triggers running, the 35 Day group should never run the most since the majority of this group survived, exhibited fewer glandular ulcers, and in general exhibited less irritative effects of the stomach.

EXPERIMENT 2

Experiment 2 was designed to elucidate the role of

ulcer formation in the development of enhanced locomotor activity. When Houser et al. (1975) reduced severity of ulceration through administration of metamide, running activity also appeared to be reduced. In addition, Tsuda et al. (1981) reported that divided feeding schedules drastically decreased running activity and the severity of glandular ulceration. These effects could presumably be due to decreased amount of gastric acid secreted into a relatively empty stomach over a 24 hour period (Hamilton, 1969). When the above two studies are considered with the role that an empty stomach has in exacerbating ulcer development (Wozniak & Goldstein, 1980), it appears that both running activity and ulcer severity increase as a function of stomach emptiness. The rat may increase wheel running activity as its stomach becomes progressively more empty in an attempt to combat behaviorally the irritation of the stomach caused by the increased secretion of gastric acid associated with food deprivation. Therefore, if the initial irritative effects of high gastric acid secretion can be inhibited effectively or reduced substantially, increased activity should not be triggered.

Rationale for Cimetidine Injections

Although many hypotheses have been postulated, hypersecretion of gastric acid has been repeatedly

implicated as the primary source of irritation which triggers ulcerogenesis (Wright, 1965). Historically, the treatment of glandular ulcers has focused on the administration of antacids, anticholinergic drugs, and other substances thought to inhibit gastric acid secretion. Due to the non-specificity of effect of the inititial anti-ulcer drugs, both toxic and numerous side effects plagued treatment programs.

More recent investigations have demonstrated the role that H2-histamine receptors play in the regulatory control of gastric acid secretion and mucosal blood flow (Lee & Tasman-Jones, 1978). Consequently, with the development of histamine receptor antagonists, these H2-receptor antagonists soon became the agent of choice for the treatment of peptic ulcers. Earlier attempts indicated that some H2-antagonists were impractical to use for clinical treatment. The use of burimamide and metiamide, both histamine antagonists, was complicated by difficulties in administration and the possibility of toxic side effects (Pare et al., 1978).

Further refinement of histamine antagonists led to the development of cimetidine (Tagamet) and ranitidine, which are now used clinically to treat peptic ulcers. Both cimetidine and ranitidine act fairly specifically at the receptor sites of the stomach and do not appear to

result in any adverse side effects (Lauterbach & Mattes, 1978). For the present study, cimetidine was chosen to be used over ranitidine because of ease of availabilty and a desire to re-evaluate cimetidine's effectiveness during an activity-deprivation procedure.

Experimentally, cimetidine has been shown to be effective in inhibiting gastric acid secretion during in vitro clinical trials and has shown to be effective in preventing glandular ulceration during behavioral testing. When cimetidine was placed on H2-receptors of guinea pig atrium and rat uterus, histamine induced gastric acid secretion was inhibited; Hl-receptors have not been demonstrated to be selectively inhibited by administration of cimetidine (Broughton & Morris, 1982; Lauterbach & Mattes, 1978; Lee, & Tasman-Jones, 1978; Soldato, 1982). In vitro trials on the action of cimetidine have demonstrated a depression of gastric acid secretion for up to 3 hours following application (Soldato, 1982). In a series of studies, Pare et al. (1978) tested the effectiveness of cimetidine in suppressing basal secretion of gastric acid and its effectiveness in blocking the formation of glandular ulcers. In behavioral testing, injections of cimetidine effectively lowered gastric acid secretion for 2 to 3 hours. Injections administered prior to restraint stress

were effective in reducing ulceration; but injections of cimetidine were not effective during an activity-deprivation experiment in blocking the formation of glandular ulcers when cimetidine was administered during the 14 hour period following the feeding hour (Pare et al., 1978).

Although cimetidine is a potent H2-receptor antagonist, it is not known if its antiulcerogenic properties are achieved through decreasing gastric acid secretion. Some investigators claim that cimetidine reduces gastric acid and pepsin secretion through its action on parietal cells and thus prevents the release of gastric acid (Lee & Tasman-Jones, 1978; Lauterbach & Mattes, 1978). Other researchers proposed that cimetidine may reduce gastric output at high levels of stress but does not affect secretion during mild stress or affect basal secretion rates (Broughton & Morris, 1982; Hemmer, Schwille, Schellerer, & Hofman, 1980). Integration of the above hypotheses has led to the suggestion that cimetidine may reduce ulceration through decreasing gastric acid secretion but other mediating factors, such as decreased mucosal blood flow (Hemmer et al., 1980), may be the cause of decreased ulceration and not simply a decrease in the secretion of gastric acid. Although the precise physiological mechanisms of the

action of cimetidine are still being debated, clinical application of cimetidine has proven to be an effective treatment for peptic ulcers.

Cimetidine was chosen to be injected during the 6 hour period prior to the 1 hour feeding session. Times for the administration of cimetidine were scheduled in an attempt to provide the most effective protection for an empty stomach from the deleterious process of ulcerogenesis. Diverse reports by previous investigators indicated that a relatively empty stomach was crucial in the formation of gastric lesions during "stress" procedures such as refrigeration, restraint-stress, or shock (Glavin & Mikhail, 1976a, 1976b; Goldstein & Wozniak, 1979; Pare, 1980). An empty stomach also appeared to be a prerequisite for the formation of glandular ulcers developed during activity-deprivation procedure. For example, glandular ulcers did not form when the animal was maintained on an ad lib feeding schedule (Glavin & Mikhail, 1975; Pare & Houser, 1973). Tsuda et al. (1981) subjected animals to an activity-deprivation procedure but fed animals in either a single session or in 2 divided feeding sessions. Animals which were fed twice a day did not run excessively and food intake was not significantly different between animals fed in one session or in 2

divided sessions. The maximum time intervals between feeding sessions were 6 1/2 and 16 1/2 hours. Therefore, the results reported by Tsuda et al. (1981) suggest that residual food in the stomach may be effective (for at least 16 1/2 hours) in buffering the stomach from the pathological agents of ulcerogenesis.

In an activity-deprivation procedure, an empty stomach appears to serve as an impetus for both ulcer formation and running activity. Although limited, several investigators suggest that the physical properties of bulk in the stomach serve a protective function from gastric acid induced ulceration (Mikhail & Hirschberg, 1972). Hamilton (1969) suggested that feedback from an empty gut triggered the animal to run. Therefore, in an activity-deprivation experiment, it is possible that an animal initially begins to run as the stomach becomes emptied of residual bulk and irritated by the increased gastric acidity associated with food deprivation. If gastric irritation acts as an afferent trigger for activity, blockage of stomach discomfort should initially decrease running activity during the time when the stomach is most empty.

As stated earlier, Pare et al. (1978) administered cimetidine to animals subjected to the activity-deprivation procedure in an attempt to block the

formation of ulcers. Results indicated that there was no significant reduction in either ulcer number or ulcer length when dosages of 20 mg, 50 mg, and 100 mg, were administered three times daily. In the Pare et al. (1978) study, injections were given 3 times daily during the 14 hour period immediately following the 1 hour feeding period. Cimetidine has been shown to be an effective gastric acid inhibitor for up to 3 hours following treatment (Pare, 1978). Therefore, in the Pare et al. (1978) study, there remained a period of 6 1/2 hours prior to the feeding session when the stomach was at its emptiest and when no anti-ulcerogenic substance remained to protect the relatively empty stomach. Thus, perhaps the injections administered by Pare et al. (1978) were not effective in protecting the stomach from ulcers because the ulcers were forming at a time after any benefits could be derived by treatment with cimetidine. In the present activity-deprivation experiment, cimetidine was injected twice during the 6 hour period prior to the one hour feeding session in an attempt to re-examine the anti-ulcerogenic effectiveness of cimetidine in the activity-deprivation situation.

METHOD

Subjects and Apparatus. Animals for Experiment 2 consisted of 14 female rats. Animals ranged in weight

from 190 to 270 grams at the start of the experiment and were approximately 60 to 80 days old. Temperature and relative humidity in the room where activity cages were housed were recorded daily. The light cycle in the activity room was a normal light/dark cycle with lights going on at 7:00 A.M. and turning off at 7:00 P.M. The apparatus and time periods used in Experiment 2 were identical to those used in Experiment 1.

Procedure. Experiment 2 utilized the same daily baseline procedures outlined in Experiment 1. Following the 5-day adaptation period, animals were matched on the basis of mean activity scores. From each matched pair, one animal received injections of the potent, antiulcerogenic drug, cimetidine (tradename: Tagamet) and the other animal received placebo injections of saline. Due to a limited number of wheels, the rats were tested in two squads so that 7 animals were run during each 18 day period.

Two daily injections were given to all animals living in the activity wheels between the following times: 1:00 PM-1:30 PM and 4:30 PM-5:00 PM. The cimetidine (Smith, Kline and French Laboratories, Philadelphia, PA) was mixed every 4 days in 15cc quantities for dose levels of 100 mg/kg ip. The daily amount of drug received by each animal was determined by daily body weight. The 100

mg/kg solution consisted of .75 grams of cimetidine, 3.4 ml of 1.00 N HCl, 6.2 ml of .1 N NaOH, and 2.5 ml of water. Each solution was adjusted to a pH of 6.0 with either .1 N NaOH or 1.0 HCl and filled to solution with .9% saline. Placebo injections consisted of .9% saline and the amount administered to each animal was also based on daily body weight.

Time and criterion for sacrifice of the animals were the same as outlined in Experiment 1. Rating of ulcer severity was also identical to the procedure reported in Experiment 1.

RESULTS

Behavioral

Daily injections of cimetidine appeared to influence the pattern of running activity seen during the course of the activity-deprivation procedure. As can be viewed in Table 6, animals were initially matched on mean baseline running rates; no significant differences in running during any of the 3 time periods for cimetidine and saline animals were recorded during ad libitum feeding. While on ad libitum feeding, animals ran the most during the 8:30 PM to 3:50 AM night period and ran the least amount during the daytime period occuring from 11:10 AM to 6:30 PM. Table 7 illustrates that a greater number of cimetidine animals were more likely to survive the rigor

of the experimental schedule, but cimetidine animals reached peak day somewhat faster than did placebo injected animals.

Insert Tables 6 and 7 about here

Upon entry into the activity wheels and the initiation of restricted feeding, both cimetidine and saline animals ran close to baseline values recorded during ad libitum feeding for all 3 time periods (see Figure 10). Figure 11 illustrates that over the first 5 days of the testing period, saline animals ran more during the 11:10 AM to 6:30 PM time period than did cimetidine animals. Rats in the cimetidine group ran only slighly higher than previously recorded baseline running values.

Insert Figures 10 and 11 about here

Although a between group analysis of variance on percent change scores was not significant, saline animals tended to run more than cimetidine animals on peak day (see Figure 12). A repeated measures analysis of variance of percent change scores across baseline, Day 1, and peak day, for the 11:10 AM to 6:30 PM period

Table 6

Mean Baseline Activity (in revolutions per day) of Animals Receiving Injections of Cimetidine or Saline

		Time Period		
Condition	n	8:30 PM.- 3:50 AM.	3:50 AM.- 11:10 AM.	11:10 AM.- 6:30 PM.
Cimetidine	7	891	476	127
Saline	7	962	442	84

Table 7

Mean Number of Days until Peak Activity for Victims and Survivors Receiving Injections of Cimetidine or Saline

		Days until Peak	
Group	n	Mean	S.E.M
Cimetidine			
Victims	3	5.7	0.98
Survivors	4	18.0	--
Saline			
Victims	5	9.0	1.72
Survivors	2	18.0	--

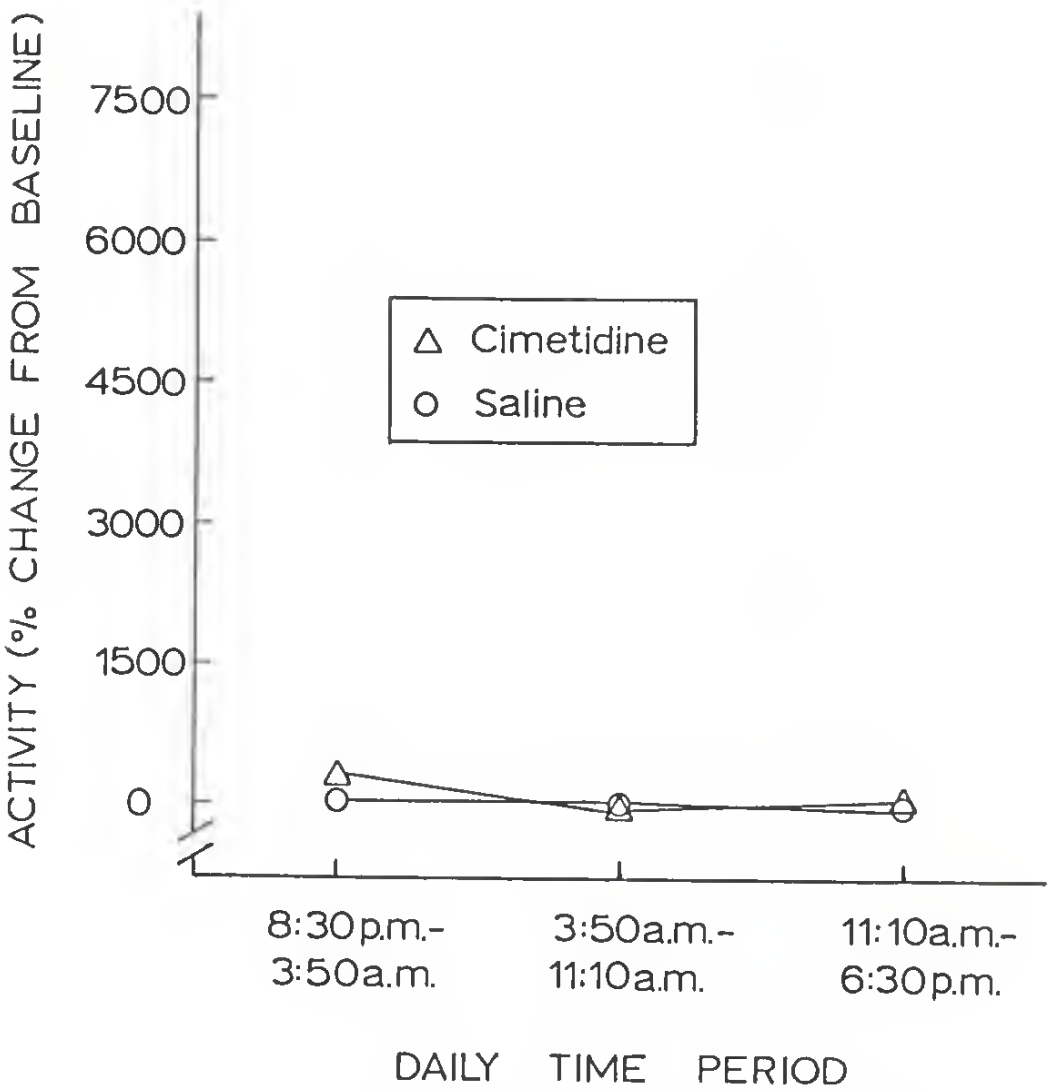

Figure 10. Percent change from baseline activity recorded during three daily time periods on day 1 for animals receiving injections of cimetidine or saline.

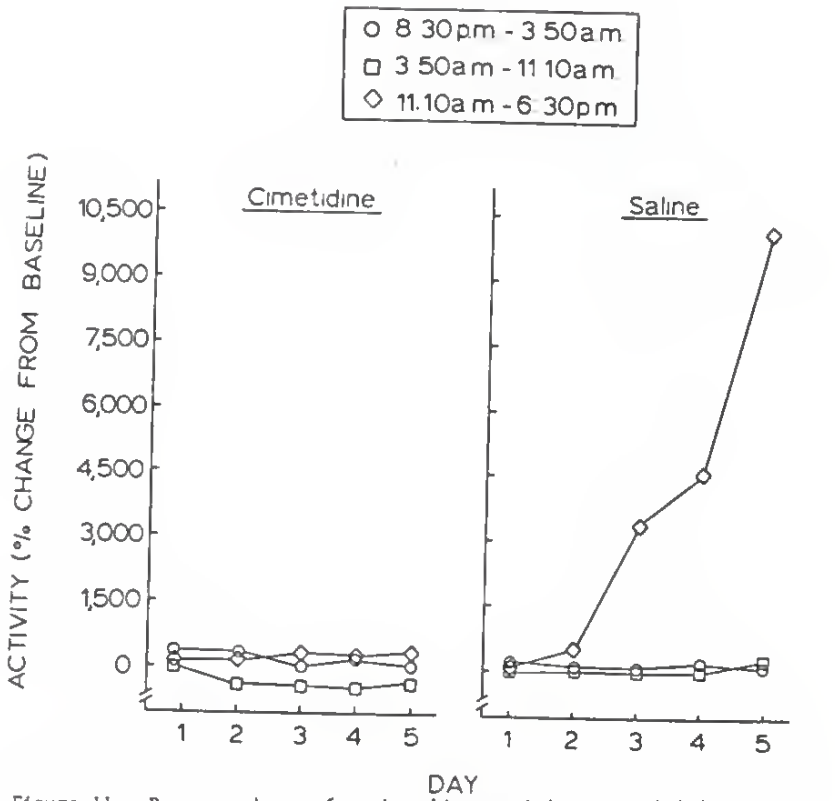

Figure 11. Percent change from baseline activity recorded during three daily time periods over the first five days for animals receiving injections of cimetidine or saline.

indicated a significant effect due to time for the cimetidine animals (F (2,12) = 8.73, $p \leq .01$) and a trend towards significance for the saline animals (F (2,12)= 2.76, $p \leq .10$).

Insert Figure 12 about here

Between group analyses of variance indicated that there were no significant differences between cimetidine and saline animals in the amount of food consumed (see Table 8), amount of water consumed (see Table 9), and the amount of body weight lost (see Table 10). Both cimetidine and saline animals ate more food as days on the restricted feeding schedule passed. A repeated measures analysis of variance indicated that saline animals drank less water on peak day than on Day 1 or during baseline measurements (F (2,12) = 6.07, $p \leq .01$). There was no significant effect over days for the consumption of water by cimetidine animals. Finally, both cimetidine and saline animals lost similar amounts of weight over the course of the 18 day activity-deprivation schedule.

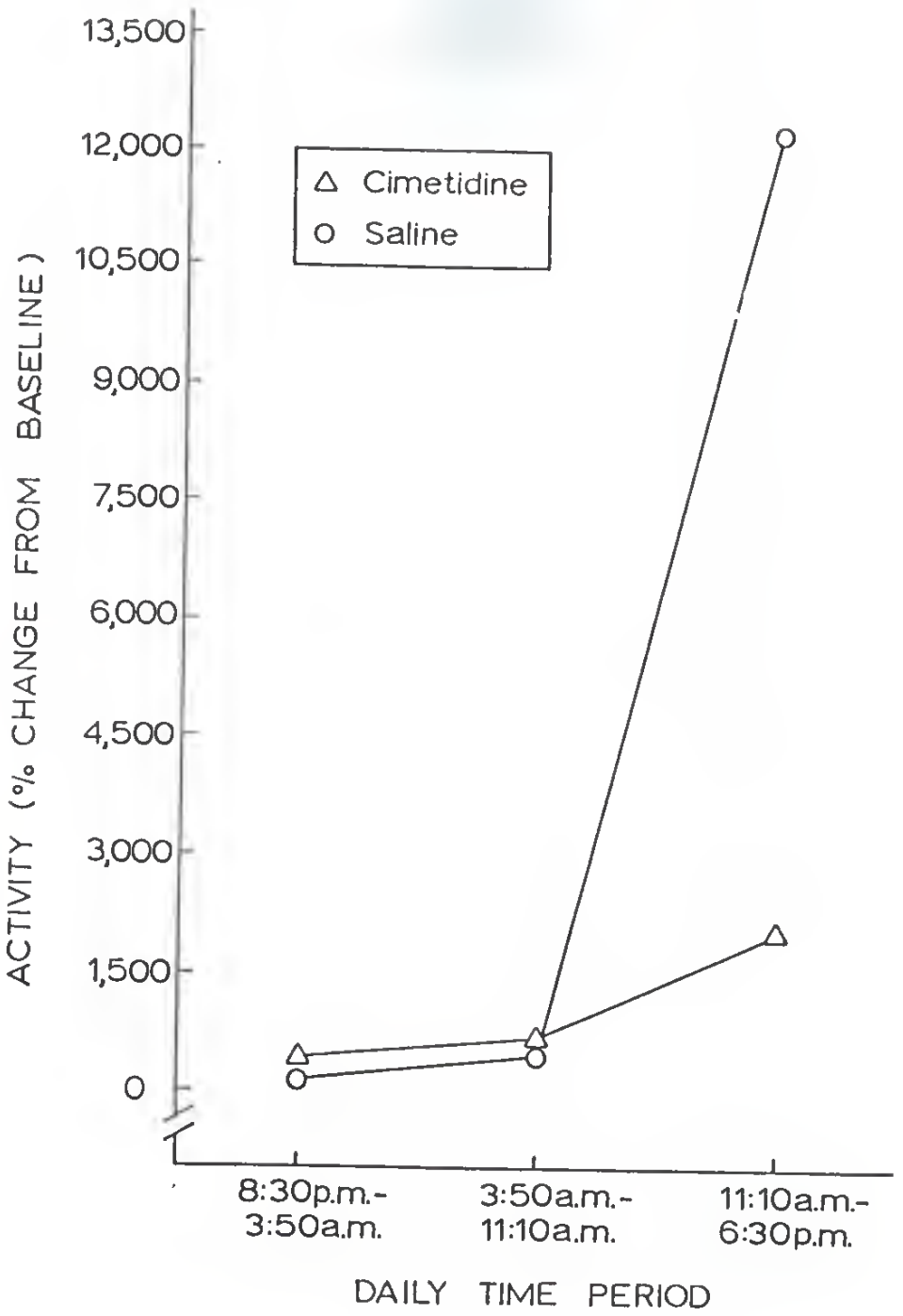

Figure 12. Percent change from baseline activity on peak day recorded during three daily time periods for animals receiving injections of cimetidine or saline.

Insert Tables 8, 9, and 10 about here

Behavioral Observations. Behavior of the cimetidine and saline animals was similar to the behavior exhibited by animals in the 0 Day group of Experiment 1. The only noticiable difference between the cimetidine animals and the saline animals was that the former tended to sleep more during the daylight hours than did the saline animals, who were usually awake and were often running on the activity wheel.

Glandular Ulceration

Results indicated that daily injections of cimetidine reduced the severity of glandular ulceration produced during the activity-deprivation experiment (see Figure 13 and Figure 14). Animals injected with cimetidine had significantly fewer ulcers than animals injected with saline (t (12) = -2.98, $p \leq .01$). The tendency for cimetidine animals to have smaller lesions than saline animals was marginally significant (t (12) = -1.97, $p \leq .07$).

Insert Figures 13 and 14 about here

Gross Pathological Observations. Both cimetidine

Table 8

Mean Amount of Food Consumed by Animals Receiving Injections of Cimetidine or Saline

		Period		
Condition	n	Baseline	Day 1	Peak
Cimetidine	7	18.7	3.8	11.1
Saline	7	16.3	5.1	11.7

Table 9

Mean Amount of Water Consumed by Animals Receiving Injections of Cimetidine or Saline

		Period		
Condition	n	Baseline	Day 1	Peak
Cimetidine	7	40.7	47.5	34.1
Saline	7	45.5	57.6	23.2

Table 10

Mean Body Weight of Animals Receiving Injections of Cimetidine or Saline

		Period		
Condition	n	Baseline	Day 1	Peak
Cimetidine	7	238	269	194
Saline	7	227	255	187

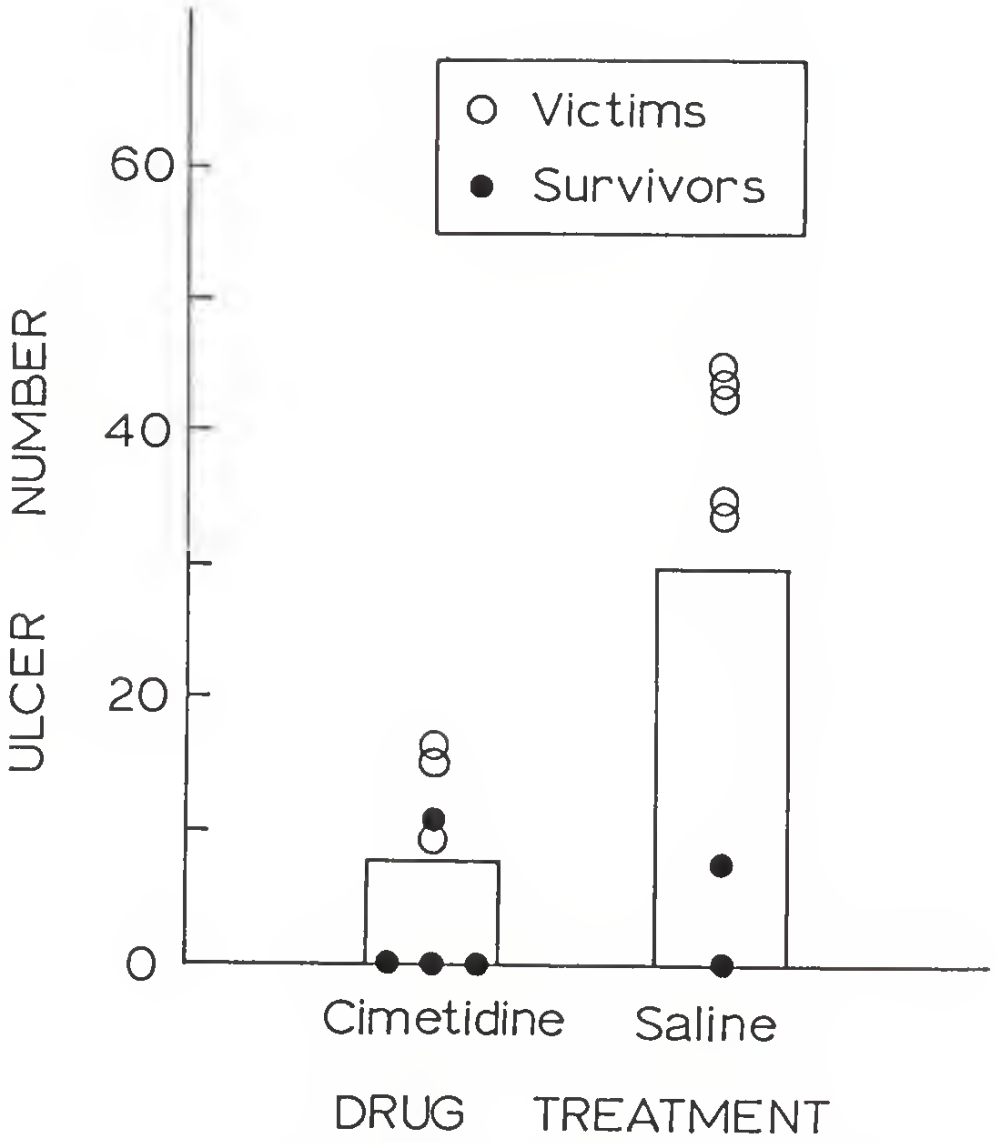

Figure 13. Mean number of glandular ulcers for victims and survivors of animals receiving injections of cimetidine or saline.

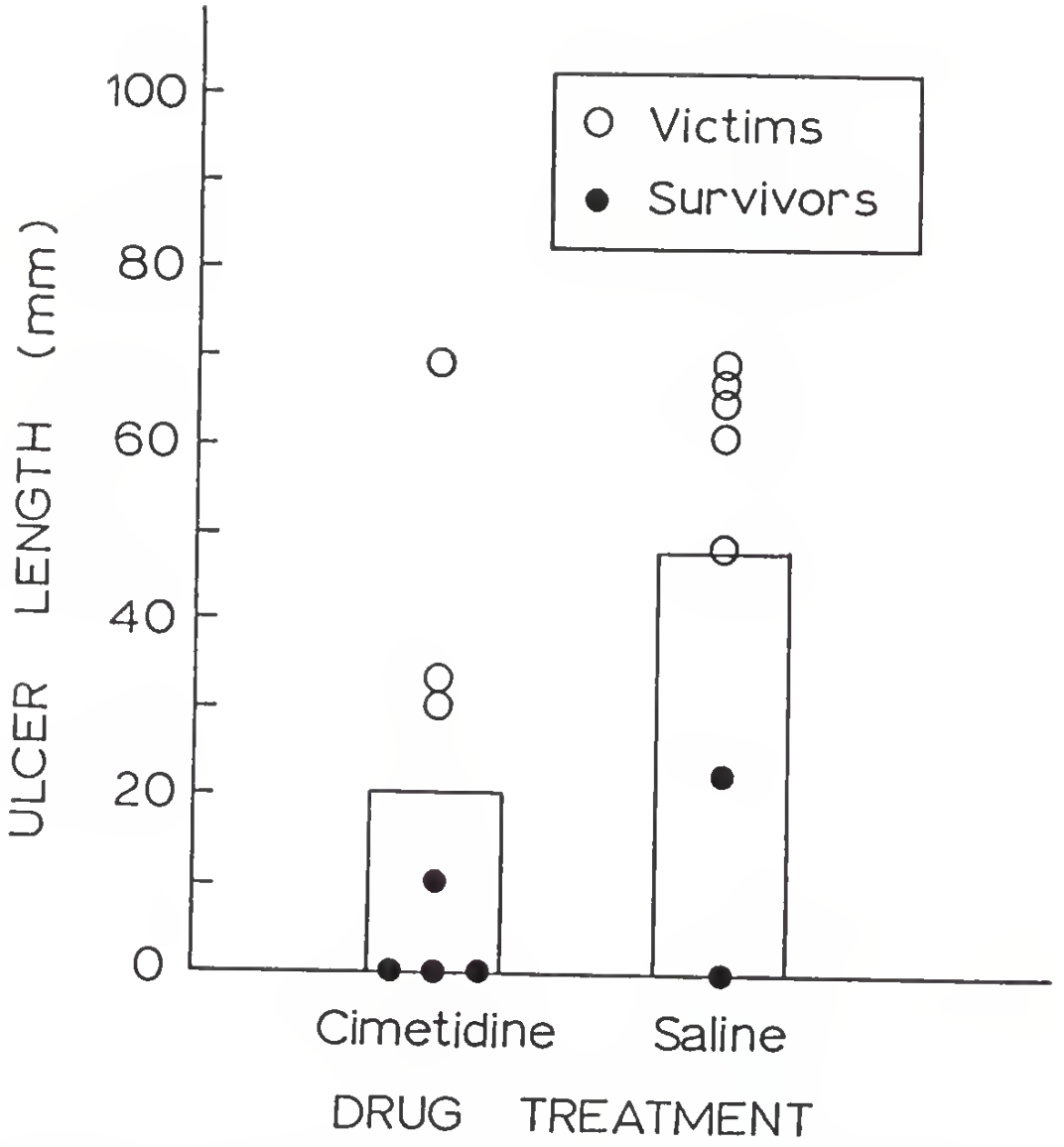

Figure 14. Mean glandular ulcer score (in mm) for victims and survivors of animals receiving injections of cimetidine or saline.

and saline animals had reduced, but similar, number of folds remaining in the corpus of the stomach. Occasionally, either a cimetidine and/or saline animal displayed hemorhages, pathology not typically classified as ulcers (Manning et al., 1978), within the glandular walls of the stomach. In both cimetidine and saline ulcerated victims, gastric pathology ranged from severe to mild ulceration. The stomachs of cimetidine animals differed from the stomachs of saline animals in that the cimetidine animals had more visible mucous membrane remaining on the glandular portion of the stomach. In addition, the intestines of cimetidine animals were usually only partially dark and of a lighter color than the inky, dark intestines of the saline victims. In the both cimetidine and the saline groups, the livers and spleens appeared slightly smaller and the adrenal glands appeared larger than animals not given access to the running wheel.

DISCUSSION

Glandular Ulceration

Results from Experiment 2 indicated that daily dosages of cimetidine substantially reduced the severity of glandular ulceration produced during an activity-deprivation procedure. In contrast to the results reported by Pare et al. (1978), the ulcer data

illustrate that both the cimetidine survivors and the cimetidine victims had fewer and smaller ulcers than did the saline survivors and victims, thus suggesting that cimetidine served some protective function against glandular ulceration for all animals receiving the anti-ulcerogenic drug. The effectiveness of cimetidine in the present experiment is consistent with other experimental findings concerning the anti-ulcerogenic properties of cimetidine, and it is suggested that the benefits derived from the cimetidine treatment can be attributed to the time of day that injections were administered.

The reduction of glandular ulceration observed in the cimedidine animals suggests that the physiological mechanisms underlying the process of ulceration in the activity-deprivation procedure are similar to the physiological mechanisms underlying glandular ulceration induced by other "stress" procedures. Desiderato et al. (1974) suggested that glandular ulceration was a result of parasympathetic activity rebounding from a state of high sympathetic activity induced at the time shock was applied to the animal. Previous research indicated that the degree of satiation at the time of high sympathetic activity induced by "stress procedures" was also a crucial factor in determining whether glandular ulcers

formed (Glavin & Mikhail, 1976b; Wozniak & Goldstein, 1980).

The amount of food in the stomach may also play a role determining when and if glandulars ulcers form during an activity-deprivation procedure. Sympathetic activity induced by daytime running may lead to a parasympathatetic rebound of gastric acid released into a relatively empty and hyperacidic stomach. If the process of ulcerogenesis is occurring during the daytime when the stomach is most empty, it is reasonable to assume that injections of cimetidine administered during the 6 hours prior to the feeding hour would be effective in preventing the development of ulcers. It is also possible to reconcile the inability of cimetidine to block ulceration in the Pare et al. (1978) study if an empty stomach is crucial to ulcer formation. It can be inferred that when Pare et al. (1978) administered cimetidine following the feeding hour, the drug had no effect on ulcerogenesis because ulcers were not developing at the time that the stomach was fairly satiated and buffered from the ulcerogenesis process by the bulk content of the stomach.

The decrease in water consumed by saline animals also might have contributed to the development of glandular ulceration. Pare (1965) reported that

prolonged exposure to stress disrupted the homeostatic regulation of water intake, so that less water was consumed by a rat under "stress." Furthermore, reduction in the ingestion of water has been associated with the development of glandular ulceration (Jaffe & Desiderato, 1978), but no conclusive statement concerning water intake in the present experiment can be made.

In the present experiment, the inability of cimetidine to protect completely all animals from ulceration implies that ulceration may begin to occur prior to the first injection of the day and indicates that individual differences are a factor in determining which animal survives. It is hypothesized that if additional injections were administered sooner than the 6 hours prior to the feeding hour, cimetidine would be more effective in blocking ulceration.

Clinical Implications. The results of the present experiment suggest that, to gain the full benefits of cimetidine treatment, the drug should be taken at times when the stomach is relatively empty. The Pare et al. study (1978) study demonstrated that administration of cimetidine did not tend to reduce ulceration if it was administered at the times that the stomach was full, following meal times; Experiment 2 indicated that cimetidine was beneficial if administered at the time

that the stomach would be most empty. The present results could have implications for treatment of peptic ulcers in humans. Directions enclosed with Tagamet prescriptions recommend taking the drug at mealtimes and also contain the information that cimetidine's protective action lasts for approximately 2 to 3 hours. If the mechanisms of glandular ulceration in rats are similar to ulceration in humans, then the present results suggest that the medication should not be taken at meal times if the full benefits are to be derived by cimetidine treatment.

Behavioral

Results from the present experiment indicated that cimetidine treatment influenced the daily pattern of running activity, as well as significantly reducing ulcer severity and increasing survival rate. Analysis of the increases in percent change scores of running during the first five days and during peak day showed that animals receiving injections of cimetidine only increased running during the 11:10 AM to 6:30 PM period in the latter portions of the 18 day experimental period. In contrast, animals receiving injections of saline showed drastic increases in running within the first five days of the activity-deprivation schedule and during peak day. Indeed, due to the extremely drastic increases in running

by two of the saline animals, the within group variance became so large that no statistically significant effect for either within or between anaylsis could be obtained with seven rats in a group. For both cimetidine and saline animals running during the remaining time periods did not appear to be affected by maintenance on the activity-deprivation schedule. Once again, increases in running during the third time period appear to be a result dependent on food deprivation; but what determines the survival of any individual seems to be the current physiological status of the rat.

If the process of ulcerogenesis is inferred to be occuring during the last time period, this suggests that the degree of stomach comfort may serve as an impetus for the animal to run. Saline animals increased drastically their running rates during the last time period, whereas animals receiving injections of cimetidine increased their daytime running rates only slightly above baseline values. These results may be explained by the following postulated sequence of events: When both the cimetidine and saline animals entered the wheel, the stomachs of both groups were probabaly relatively full due to maintenance on the ad libitum feeding schedule; as a result, running rates for all time periods on Day 1 were close to baseline values. Due to the unfamilarity with

the deprivation schedule, all animals consumed relatively small amounts of food on the first meal experienced in the activity wheels. The small amount of food consumed may have failed to maintain normal bulk levels in the stomach from one feeding hour to the next. As with humans who complain of hunger when first starting a diet, the rats may also feel the discomfort of hunger pangs or a churning of the stomach, presumably induced by secretions of gastric acid and other agents associated with ulcerogenesis into an empty stomach. If normal levels of running were maintained during the first and second time periods, there may have come a time when the level of running induced a parasympathetic response which was perceived as irritable due to the lack of physical bulk present in the stomach and any subsequent parasympathetic activity resulting from the sympathetic activity of running.

The dramatic increases in running viewed during the 11:10 AM to 6:30 PM period, accompanied by the lack of change in running during the remaining two time periods, support the notion that animals may initially attempt to counter bouts of stomach irritation with bouts of high activity. If gastric acid is released into an empty stomach following nighttime running, stomach discomfort may serve as an afferent trigger to start running in an

attempt to regulate behaviorally the degree of stomach comfort. The relatively small increases observed over the first 5 days for the cimetidine animals suggests that there was no need to combat behaviorally stomach discomfort due to the drug intervention with cimetidine. Treatment with cimetidine may have served to keep the degree of stomach irritation within a normal range, thereby not acting as an impetus for the animal to run.

GENERAL DISCUSSION

The answer to the question as to why rats on a restricted feeding schedule run excessively still remains elusive. It can be logically inferred that some aspect about switching the animal from an ad libitum feeding schedule to a restricted feeding schedule primes the rat to run excessively if the outlet of an activity wheel is made available. Furthermore, the interactive effects of physical activity with food restriction appears to be the ultimate combination which propels the rat into an endless circle of activity.

In the present set of experiments, the major increase in running occurred during the time period farthest away from the last feeding session, while running during the remaining two time periods was relatively unaffected. Although the following hypothesis is merely speculative, it remains plausible to assume

that some direct or indirect gastric consequence of eating less food each day triggers the animal to expend excessive amounts of energy during a time when energy should be conserved and at a time when the animal had been previously sleeping. The precise reason why the ingestion of smaller quantities of food per day would trigger such maladaptive energy expenditure is perplexing.

In Experiment 1, the pre-adapted animals increased running the most during the last time period but also survived the longest with less gastric ulceration. Therefore, the postulated state of an aversive gut may not be the sole reason why animals run so much. Another gastric hypothesis postulated to account for exaggerated wheel running is a purely involuntarily response to food restriction; this could be mediated by gastric consequences or by any of the other myriad of possibilities which are resultant from food restriction and physical activity. Finally, the less ulceration in the pre-adapted groups might indicate that running and ulcerogenesis are unrelated causally with either glandular ulceration or exaggerated running being produced as an epiphenomena to the combined schedules of food restriction and activity.

In the second experiment, animals receiving

injections of saline drastically increased running above baseline values over the first five days, whereas in the majority of the animals in the 0 Day Group (Experiment 1) only began to increase running during the last time period after the passage of approximately 3 to 7 days. Thus, purely the lack of residual bulk remaining in the stomach cannot be the sole reason for triggering excessive wheel running. It is possible that that the "stress" of the daily injections increased environmental stimulation and induced those animals to begin to run sooner than the 0 Day group (note that at least 2 days on the activity-deprivation schedule passed before most of the animals in the saline group began to increase running during run the last time period).

In reality, the hypothesized notion of stomach comfort is an empirically untestable notion in laboratory rats and is open to the same criticisms leveled against any hypothetical construct in psychology. Ideally, and in conjunction with self-reports from humans, enough empirical evidence may be gathered to either accept or reject confidently the notion of stomach discomfort as an early impetus for exaggerated wheel running in laboratory rats.

Role of the Central Nervous System

Taken together, the results from the present set of

experiments support the hypothesis that gastric irritation may serve initially as an impetus to run; the results also imply that additional physiological processes, resulting from the interactive effects of activity and food restriction, mediate excessive wheel running during latter portions of the activity-deprivation schedule. Due to the progressive survival rate and the progressive increase in daytime running observed in pre-adapted groups and in animals receiving injections of cimetidine, it is suggested that the elevation in running observed during the 11:10 AM to 6:30 PM time period is initially the result of behavioral regulation of stomach discomfort, and later the result of concomitant changes in the functioning of the central nervous system.

Norepinepherine synthesis and uptake have been reported to increase in the hypothalmus, amygdala, and other telencephalic structures during the activity-deprivation procedure (Tsuda et al., 1982b) and during other ulcerogenic procedures (Anisman, Pizzino, & Sklar, 1980; Cassen, Roffman, Kuruc, Obrsulak, & Schneider, 1980; Henke, 1982). Several investigators have suggested that changes in the usage of central NE is an adaptive mechanisms in response to stress or prolonged sympathetic stimulation (Goldstein, Sauter, Kigotaka, &

Fuxe, 1980; Henke, 1982). Bhagart, Young, and Biggerstaff (1977) reported that synthesis of NE is increased on a short-term basis in response to immediate, physiological demand and is increased on a long-term basis, via a separate mechanism, in response to prolonged sympathetic stimulation or stress. If stimulation is further prolonged, a reduction of central stores of NE becomes evident (Anisman et al., 1980; Tsuda et al., 1982b).

In the activity-deprivation experiment, long term changes in the production of NE may account for the excessive and tenacious wheel running observed during times of starvation. The catecholaminergic system has been routinely associated with locomotor arousal and with highly stereotyped activity (Murphey & Nagey, 1979). Although short-term increases in NE synthesis occur during stress procedures (Bhagart et al., 1977) and during food deprivation (Campbell & Fibinger, 1971), it may not be until activity is experienced and long-term adaptation mechanisms take over that increases in NE production become influential or overriding during the activity-deprivation procedure. For example, home cage control animals do not appear to become more hyperactive and more agitated as days on the restricted feeding schedule pass. Activity animals appear to become

increasingly more hyperactive as each individual's peak day draws nearer.

The higher running rates, combined with the higher survival rates and the reduction in ulceration observed in the 25 and 35 day pre-adaptation groups, suggest that changes in a central mechanism may trigger excessive running during latter portions of the activity-deprivation experiment. The lower incidence of ulceration in the pre-adapted groups suggests that a progressive increase in gastric discomfort cannot account solely for the elevated running observed during daytime periods. Correspondingly, because pre-adapted rats increase running only during the time period farthest from the last feeding session, gross changes in NE levels cannot account solely for increases in running observed for only one time period. For example, Tsuda et al. (1982b) reported that the increased utilization of NE is sustained for at least 5 days during an activity-deprivation procedure. If changes in NE triggered excessive running indiscriminantly, increases in running during the night should also be observed. Therefore, perhaps through a combination of stomach emptiness and NE synthesis, excessive wheel running is induced.

The delayed increase in running observed in the rats

receiving cimetidine treatment may also be indicative of NE induced arousal. On peak day, cimetidine rats which were ulcer free showed elevated running during the daytime running period, whereas those same rats had been previosuly sleeping at the beginning of the experiment during the last time period. The reduced ulceration in cimetidine animals indicates that treatment was still effective in buffering the stomach from the irritative effects of ulcerogenesis, so the increased running during the latter periods must be the result of some other physiological outcome of physical activity and food restriction. In the present set of experiments, the factors of stomach emptiness, gastric discomfort, and long-term NE changes can only be inferred, and additional research is needed to assess directly the factors which induce the food restricted animal to run so much.

Excessive Wheel Running: An Adaptive Environmental Response?

As discussed earlier, excessive wheel running can be viewed as maladaptive because what the rat does leads to its own death. Results from Experiment 1 imply that excessive activity may not be so self-defeating when it is considered in the rat's natural environment versus the artificial environment of the laboratory. In other words, perhaps heightened activity is beneficial to the

rat because it would increase the probabilty of finding food in the natural environment but has no effect on the probabilty of finding food in the experimentor's controlled environment. The number of days until peak required for the 0 Day Group suggests that excessive running does not immediately lead to ulcer formation. In the rat's natural environment, 12 days represent a rather lengthy period of survival time on minimal food and high activity. Therefore, the increased activity during the daytime may represent an evolved or built-in system for increasing the probabilty of finding food.

If increased running is behaviorally regulated initially, there may come a time as the enforced schedule is prolonged, when a point of diminishing returns is reached; central nervous system mechanisms may subserve behavioral regulation and propel the animal into a festinating frenzy of activity which is regulated by a positive physiological feedback loop. Although excessive wheel running may serve as a parody of what actually occurs in the natural environment, the activity-deprivation phenomena may elucidate underlying adaptive mechanism not normally viewed in the rat, as well as shedding insight into the strange and paradoxical condition of anorexia nervosa.

Excessive Wheel Running and Possible Relationships to Anorexia Nervosa

Behavioral Profile. The activity-deprivation situation may serve as a potential model for the condition of anorexia nervosa in humans. In both situations, a restriction of food intake is accompanied by vigorous, stereotyped activity which results in maladaptive energy expenditure in the face of starvation. Both the behavioral progression and the physiological profile viewed in rats on an activity-deprivation schedule are also characteristically viewed in the human anorexic.

Although it is impossible to separate the cognitive components affiliated with anorexia nervosa, it is the contention of this investigator that the exercise and diet regimen, initially regulated behaviorally in humans, eventually results in the same type of physiological feedback loop which propels the activity-deprivation rat into a furious circle of activity. Casper and Davis (1977) reported that anorexics typically follow a sequence of phases enroute to becoming trapped in the anorexic attitude. In the beginning, anorexics are slightly overweight (approximately lo to 15 pounds) and report that the

initial loss of weight is satisfactory. After losing approximately 10 pounds, the majority of individuals report feeling hungry but easily counteract feelings of hunger by exhausting themselves with exercise.

In contrast to individuals who have been starved, anorexics report having more energy and engage in endless activities; individuals who are starving to death are listless and tend to conserve energy. Clinicians report that anorexics pursue activity in an obsessive manner. The type of exercise program chosen by the anorexic is highly structured and assumes stereotyped qualities. In addition to high activity, anorexics have a preoccupation with food. Often, anorexics will prepare meals and hoard food but still refuse to eat. During these earlier phases, individuals will often respond to outpatient treatment and gain weight.

After approximately a 25% to 50% loss of body weight, individuals usually are hospitalized, do not respond to treatment, but do grudgingly admit "something must be wrong." During these latter stages, anorexics are suffering from the physical effects of starvation. Amenorrhea, dizzy spells, muscle weakness, hypothermia, insomnia, and changes in the skin and hair are characteristic. Individuals still do not admit to being thin and are surprisingly alert for their extremely

debilitated physical condition. Clinicians also report that anorexics, when asked if they would have dieted if they knew they were going to regress into such a physical and mental state, usually replied that they would not have started the diet. Casper and Davis (1977) concluded that the negative reponse was indicative of a lack of full control over the anorexic process.

Physiological Profile. Some aspects of the physiological profile viewed in anorexics mirror the physiological profile of rats on an activity-deprivation schedule. Abnormalities associated with hypothalamic functioning, NE metabolism, adrenal activity, and gastric functioning are observed in persons with anorexic nervosa (Weiner, 1977). Most clinicians are uncertain whether hypothalamic abnormalities precipitate the disease or are the result of the physiological course of anorexia nervosa. Many investigators report that at 80% of body weight, altered NE functioning is observed routinely in individuals suffering from anorexia nervosa (Gerner & Gwirtsman, 1981). In addition, urinary measures of 3-methoxy-4-hydroxyphenyl glycol (MHPG) indicate that NE levels are low. As with the activity-deprivation animals, perhaps a depletion of central NE stores occur following prolonged sympathetic stimulation.

The disturbances in both gastric and adrenal

functioning in anorexics is also similar to the disturbances viewed in activity-deprivation animals. In anorexics, altered gastric emptying is often viewed (Holt, Ford, Grant, & Heading, 1981), and glandular ulceration can occur. Altered adrenal functioning is inferred due to elevated cortisol levels in the anorexic (Walsh, 1978).

CONCLUSION

The excessive energy expenditure by activity-deprivation rats and anorexics during times of starvation remains a paradox. In the present experiments, exaggerated activity during daylight periods only becomes apparent after a restriction in food leads to an initial decline in body weight and only if an outlet to physical activity is available. The physiological feasibility of such a biological mechanism is questionable. Why would an organism's physiology be such that with progressively declining body weights, progressively higher amounts of energy are expended? The apparent adaptive response would appear to be to conserve energy whenever possible; a response which is often viewed in animals and humans who are simply starving and not exercising. To conclude, the tenacity of the high energy expenditure by starving rats and humans, in the face of such deletertious physical outcomes,

suggests a mediation by rampant physiological processes --- an evolutionary advantage which can only be speculated upon now.

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INVESTIGATION OF EXAGGERATED WHEEL RUNNING IN ALBINO RATS: EFFECTS OF PRE-ADAPTATION TO A RESTRICTED FEEDING SCHEDULE AND DAILY TREATMENT WITH CIMETIDINE

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ABSTRACT

When a laboratory rat is maintained on a one hour per day restricted feeding schedule and housed in an activity wheel, the rat runs progressively more each day until running becomes excessive, glandular ulcers form, and eventually leads to the demise of the animal. Due to the high correlation between excessive wheel running and glandular ulceration, the hypothesis that gastric discomfort was initially triggering the animals to run was explored. Previous research indicated that if the hypersecretion of gastric acid induced by food deprivation was alleviated, ulceration caused by subsequent application of a "stressor" was also reduced. Therefore, in the present set of experiments, reduction of gastric irritation was attemped by pre-adaptation to a restricted feeding schedule or through administration of an anti-ulcerogenic drug.

In Experiment 1, animals were pre-adapted to a running wheel for 5 days, and then pre-adapted to a one hour restricted feeding schedule for either 0, 15, 25, or 35 days prior to re-entry into the activity wheels. Home cage control animals never re-entered the activity wheels but were placed on a one hour per day restricted feeding schedule. An activity animal (and its yoked control) were sacrificed at the end of the 18 day wheel period or whenever an activity animal became moribund.

The stomach was then excised and later scored for glandular ulceration.

Results indicated that increasing amounts of pre-adaptation experience reduced the number of animals which became moribund and reduced the severity of glandular ulceration. Regardless of the amount of prior experience on a restricted feeding schedule, all animals substantially increased running activity only during the time period which was farthest away from the preceding day's feeding session. Therefore, it was suggested that the degreee of stomach emptiness, or the absence of bulk, may serve as the impetus for exaggerated wheel running.

In Experiment 2, cimetidine, an anti-uilcerogenic drug, was administered twice daily during the 6 hour period prior to the 1 hour feeding session. Placebo injections of saline were administered to matched activity animals. Results indicated that animals receiving injections of cimetidine had less severe glandular ulceration than animals receiving injections of saline. Analysis of running patterns indicated that cimetidine rats showed a delayed onset of increased running during the time period preceding the feeding hour. Saline animals showed substantial increases in running throughout virtually the entire experimental period. Therefore, it was proposed that gastric

irritation of a relatively empty stomach may serve as the impetus for exaggerated wheel running during times of starvation.